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The Effects of WR242511 in Rhesus Monkeys

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13. ABSTRACT (*Maximum 200 words*)

Many substances that form methemoglobin (MHb) counter cyanide (CN) toxicity. Although MHb formers can be applied as treatments for CN poisoning, it was reasoned that a long-acting MHb former could serve as a CN pretreatment. An 8-aminoquinoline drug, WR242511, was characterized as a long-lasting MHb former, producing sufficient MHb to protect against 2 X LD_{50} of CN. Transition for development of WR242511 was based on data from rodents and beagle dogs collected elsewhere. Advanced development testing of WR242511 at USAMRICD was conducted in the rhesus monkey. WR242511 was administered intravenously (IV) to two female and four male rhesus monkeys in doses of 3.5 and/or 7.0 mg/kg, with the objective of producing protective levels of MHb. A single drug-naïve male received WR242511 PER OS at 7.0 mg/kg. Although WR242511 at these doses produced up to 22.6% MHb in beagle dogs in earlier studies conducted elsewhere, it produced little MHb (mean < 2.0%) in the rhesus monkey. Transient hemoglobinuria was noted approximately 60 min post-injection. Two lethalities occurred following the 7.0 mg/kg dose (one IV and one PER OS). Histopathology revealed multiple organ toxicity, with greater severity in the PER OS-treated animal. These findings do not support the continued development of WR242511 as a CN pretreatment.

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Table of Contents

List of Appendicies

I. Introduction and Background

Methemoglobin (MHb) formation is an effective strategy to counter cyanide (CN) toxicity (Chen and Rose, 1952; Baskin and Fricke, 1992; Rockwood et al., 1999). An 8-aminoquinoline, 8-[(4-amino-l-methylbutyl)amino]-5-(l-hexyloxy)-6-methoxy-4-methyl quinoline (DL-tartrate), hereafter referred to as WR242511 (see Figure 1), was initially targeted for its potent anti-malarial properties. However, it was discontinued as a candidate anti-malarial compound due to a significant "side-effect," *viz.*, MHb formation. Subsequently, when its MHb-forming capacity was systematically characterized, WR242511 emerged as a leading anti-CN compound (Transition Information Paper, 1994). In dogs, this compound was shown to have a long half-life and yield stable steady-state MHb levels (Marino et al., 1994). WR242511 was recommended for transition as a CN pretreatment to Milestone 1 in December 1994 (Transition Information Paper, 1994). This transition to Milestone 1 occurred in March 1995.

This report describes an advanced development project designed to evaluate the safety and behavioral efficacy of WR242511 for use as a pretreatment against CN poisoning. Rhesus monkeys served as subjects. Research was conducted at the US Army Medical Research Institute of Chemical Defense (USAMRICD), APG-EA, MD, under USAMRICD animal use protocol 1-05-98-000-A-759 (hereafter referred to as protocol 759) (Rockwood, 1998). See Appendices A and B for a list of project participants and for a complete timeline of events relevant to this report, respectively.

Various species, such as rats, mice, sheep and dogs have been used in the study of MHb formers and MHb formation, with the beagle dog being used particularly often (Bright and Marrs, 1986; Marino et al., 1994; Marrs and Bright, 1986). Beagle dogs have been used for the study of numerous classes of MHb formers, including 8-aminoquinolines, such as WR242511 (Marino et al., 1994; Levine et al., 1996), as well as aminophenones (Bright et al., 1987), and aminophenols (Bright and Marrs, 1982).

A significant portion of protocol 759 was designed to evaluate the effects of WR242511 on cognitive status in rhesus monkeys utilizing an established nonhuman primate version of the Serial Probe Recognition (SPR) task (Castro, 1995, 1997; Castro et al., 1992, 1994). The rhesus monkey was designated as the test species for two principal reasons. First, use of this species would allow for consistency across our advanced development database. Second, there was compelling evidence demonstrating the appropriateness of using rhesus monkeys in the study of 8-aminoquinolines and related compounds. For example, it is noteworthy that the rhesus monkey was the model of choice for the extensive US Army post-WWII-era evaluation of novel anti-malarials, including numerous 4- as well as 8-aminoquinolines (excluding WR242511, which had not yet been synthesized) (Wiselogle, 1946). Schmidt and colleagues demonstrated that following exposure to a large number of potential anti-malarial compounds, the rhesus monkey exhibited similar toxicological as well as neurological sequelae as reported in humans (Blanchard and Schmidt, 1946; Schmidt, 1983; Schmidt and Schmidt, 1949; Schmidt et al., 1977).

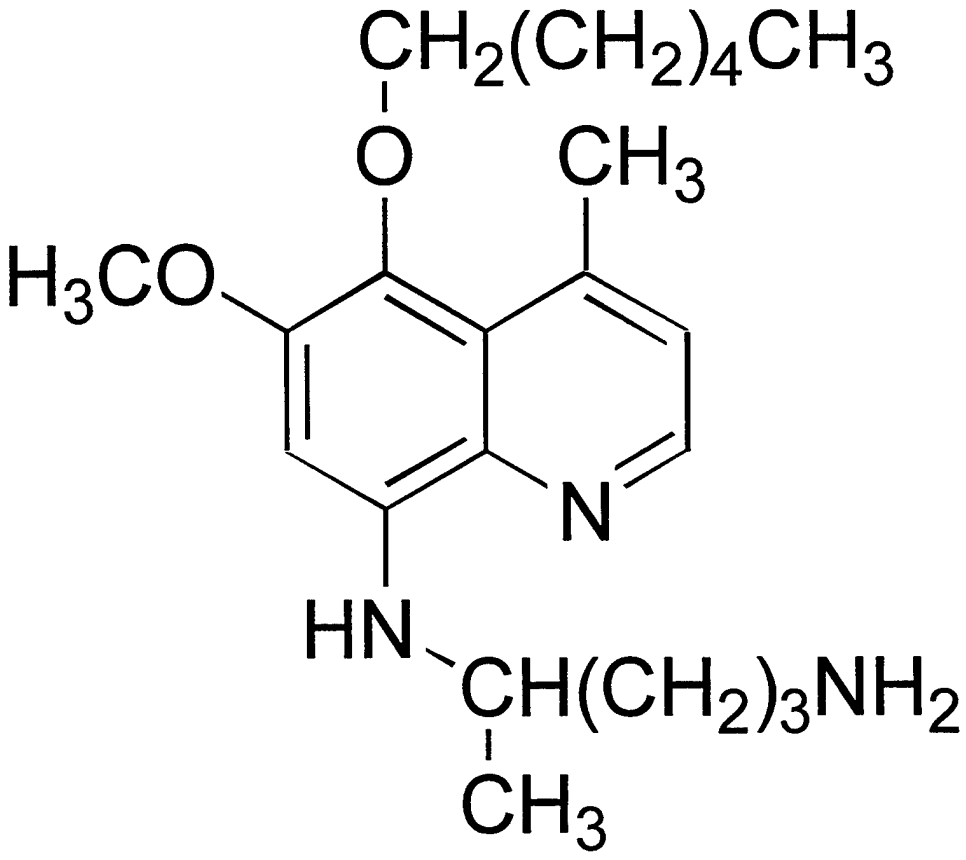

Figure 1. Structure of test compound WR242511.

II. Experimental segments in protocol 759

Original experimental segments for protocol 759 are presented in Table 1. Segment A (calibration) was designed principally as a proof-of-concept segment, to verify available information on rhesus monkey reactivity and sensitivity to MHb formers (Wiselogle, 1946; Moe et al., 1949; Martin et al., 1995) since only scant relevant information was available. [In addition, Segment A allowed for the generation of calibration equations for a non-invasive MHb monitor prototype. Use of this non-invasive MHb monitor prototype had no impact on the outcome of the research described herein and was only employed during the calibration segment of this protocol. It was not used in conjunction with WR242511. Therefore, no further discussion or description of this non-invasive MHb monitor prototype is included in this report.] The prototypic MHb former sodium nitrite ($NaNO_2$) was utilized to induce MHb during Segment A. This compound has been used experimentally as well as clinically since the 1930s as an efficacious treatment for CN toxicity and is one of the components in the DoD anti-CN kit. Following Segment A, the intention was to determine the dose range of WR242511 that yielded 5-7% MHb (Segment B). The results of Segment A are included in this report; however, the focus is on the results of Segment B. The remaining three segments depicted in Table 1 (Segments C-E) were not conducted due to severe reactions to WR242511 in rhesus monkeys, as described below. Test articles described in this report are presented in Appendix C.

Table 1. Original experimental segments in protocol 759 (Rockwood, 1998).

Segment	Procedure
A (Calibration)	- Induce MHb in rhesus monkeys using sodium nitrite (n=6) - Calibrate the Datex-Ohmeda non-invasive MHb monitor in non-SPR-trained animals - Validate the results using arterial blood samples analyzed using the OSM3 Hemoximeter
B (Preliminary dose-ranging)	- Determine dose of WR242511 that produces ~5-7% MHb - Examine time-course for MHb changes - Use animals from Segment A (n=6)
C (Preliminary challenge)	- Pretreat a subset of animals used in Segments A and B (n=2) with dose of WR242511 determined to produce ~5-7% MHb in each animal - Challenge with 2 X MLD sodium cyanide (CN), and determine protective effect of MHb against CN toxicity
D (Phase I testing -Drug Safety)	- Ascertain the individual dose of WR242511 for each SPR-trained animal (n=10), to produce a MHb level of ~5-7% - Evaluate SPR performance (vs baseline) under this level of MHb
E (Phase II testing – Behavioral Efficacy)	- Administer 2 X MLD challenge of CN to same animals used in Segment D (n=10), after pretreatment with WR242511 - Evaluate recovery and time-course of return to SPR baseline levels

II.1. Segment A

A preliminary portion of Segment A has been presented elsewhere (Rockwood et al., 1999).

II.1.a. Methodology

II.1.a.1. Animals

Six rhesus monkeys (*Macaca mulatta*) served as subjects (two females and four males). All animals were healthy and had no history of chronic illness, severe injury or exposure to MHb-forming compounds. Animal histories are presented in Appendix D. Initial average animal weights were 5.6 kg and 9.7 kg, for females and males, respectively. The following animals were tested in this segment:

P3C (Sheba)	Female
B055 (Nancy)	Female
7AS (Astin)	Male
JW0 (Joe)	Male
F942 (Kong)	Male
16999 (Byron)	Male

II.1.a.2. Procedure

All animals were tested individually. Each animal was anesthetized with 3.0 mg/kg (administered intramuscularly) tiletamine HCl/zolazepam HCl (Telazol®) and maintained on a surgical plane with isoflurane (0.5-2.0% in oxygen). An arterial catheter was placed centrally, allowing for serial blood sampling as required for hematologic evaluation.

$NaNO_2$ (prepared in 0.9% saline on the day of testing; 1.0 ml/kg) was administered intravenously (iv) in increments until approximately 15.0 % MHb was achieved, or until a maximum of approximately 20 mg/kg had been administered. Animals received a total of six or seven infusions of $NaNO_2$, with an average of 26.5 min between each infusion. Mean time between $NaNO_2$ infusion and blood sampling was 17.4 min (range: 15.8-19.8 min). Hematologic information, including MHb, as well as total hemoglobin (tHb), oxyhemoglobin (HbO_2), reduced hemoglobin (RHb), oxygen content (O_2Ct), sulfhemoglobin (SHb) were analyzed using OSM3 Hemoximeter technology (Radiometer America).

II.1.b. Results

Animals received a cumulative dose of 16.0-20.0 mg/kg of $NaNO_2$, across an average of 163 min. Baseline MHb levels were all <1.0%, with a mean of 0.45%. Maximum MHb levels observed ranged from 8.6-15.5% (Table 2). Not surprisingly, serial $NaNO_2$ injections corresponded closely with increasing MHb levels (Pearson's r values > 0.95). In addition, with increasing levels of $NaNO_2$, there were decreases in tHb, HBO_2, and

O_2Ct, as well as an increase in RHb. No changes in SHb were observed. See Appendix E for additional details pertaining to these results.

Table 2. Segment A MHb summary.

Animal	Initial weight (kg)	Cumulative $NaNO_2$ (mg/kg)	Maximum % MHb
16999 (Byron)	10.6	19.0	15.2
B055 (Nancy)	7.2	16.0	15.5
7AS (Astin)	9.2	19.2	10.5
JW0 (Joe)	8.8	19.4	9.6
F942 (Kong)	10.0	20.0	10.0
P3C (Sheba)	3.9	19.6	8.6

II.2. Segment B

II.2.a. Methodology

II.2.a.1. Animals

All six animals from Segment A also served as subjects in Segment B. An additional healthy male rhesus monkey (6VY, Adams, 12.6 kg) was also used in this segment. See Appendix A for history on 6VY. The following animals were tested in this segment:

P3C (Sheba)	Female
B055 (Nancy)	Female
7AS (Astin)	Male
JW0 (Joe)	Male
F942 (Kong)	Male
16999 (Byron)	Male
6VY (Adams)	Male

II.2.a.2. Procedures

All procedures were reviewed and approved by the Institute Animal Care and Use Committee. Animals were restraint-chair trained by USAMRICD personnel prior to testing and remained in the chair for 1 hr postinjection before being returned to their home cage. On the day of testing, animals were tested individually. WR242511 was initially prepared in PEG200 in a concentration of 7.0 mg/ml. Subsequently, WR242511 was prepared in Multisol, in a concentration of 14.0 mg/ml. Injections were administered iv, in a volume of 0.5 ml/kg, yielding doses of 3.5 and 7.0 mg/kg, using PEG200 and Multisol, respectively. Injections were administered across 2-3 min. Doses were selected based on experiments in beagle dogs, as summarized in the Transition Information Paper (1994). The iv route was selected for ease of administration, since

previous reports in beagle dogs demonstrated similar patterns of MHb formation by iv and oral routes of administration (Noker, 1994; Transition Information Paper, 1994).

Drug solutions were prepared fresh on the day prior to or on the day of use. When a solution was prepared on the day prior to use, the solution was kept in a refrigerator until the following morning. Solutions were always maintained in an amber glass vial. To facilitate solution preparation, sonication and heat were applied. In a conversation with personnel at Ash Stevens Inc. (the laboratory that synthesized WR242511 in ~1990) about solubility difficulty, it was indicated that the compound has a maximum quantitative solubility of 2.5 mg/ml in water. The solubility characteristics of this compound in PEG200, however, were unknown. However, there was little concern that sonication, heat or manually crushing the compound, to facilitate solution preparation, would adversely affect compound stability (Blumbergs, August 1998, personal communication).

During the day of WR242511 injection, venous blood samples were obtained prior to injection, and at 1, 6, 12, and 24 hr postinjection. Subsequent blood sampling occurred daily for as long as 11 days postinjection. Samples were analyzed using the OSM3 Hemoximeter. Full blood chemistry analyses were performed as needed by personnel in the Comparative Pathology Branch at USAMRICD. Urine was collected in a catch tray positioned below the restraint chair.

II.2.b. Results and Procedure Modifications

As depicted in Table 3, all animals, except one, received an iv injection of WR242511 at 3.5 mg/kg. During injection of the remaining animal, the catheter clogged, and the injection could not be completed. Therefore, this animal received 3.14 mg/kg instead of 3.5 mg/kg. Baseline levels of MHb were all <1.0%, with a mean of 0.62%. Additional hematological parameters, as well as blood chemistry, are presented in Appendix F.

Table 3. Segment B MHb summary following iv administration of WR242511 (3.5 mg/kg).

Animal	WR242511 Dose (mg/kg)	Maximum % MHb observed (time)
PC3 (Sheba)	3.5	0.9 (72 hr postinjection)
7AS (Astin)	3.5	1.5 (96 hr postinjection)
B055 (Nancy)	3.5	3.9 (48 hr postinjection)
JW0 (Joe)	3.14*	1.1 (72 hr postinjection)
F942 (Kong)	3.5	1.0 (72 hr postinjection)
16999 (Byron)	3.5	1.0 (48 hr postinjection)

*(clogged catheter)

At approximately 60 min postinjection, dark (reddish/brown) urine was observed (hemoglobinuria). The first incidence was noticed after the animal was returned to its home cage. It was not immediately clear whether the fluid was darkened urine or blood from an injury. The animal was immediately placed back into the restraint chair for examination. The veterinarian determined that there was no outward injury or irritation, and the animal was returned to its home cage. Subsequent animals also displayed hemoglobinuria at approximately the same point postinjection (60 min). The hemoglobinuria was temporary, observed during the first urination postinjection (~60 min), but not at later times. It remained unclear whether the hemoglobinuria resulted from the drug, the solvent, or perhaps from undetected irritation due to the length of time the animals remained in the restraint chair (~65 min). It is noteworthy that for several days after WR242511 injection, the blood samples drawn for analysis appeared viscous, and brown-tinged. These observed changes were more pronounced at the higher dose (see below).

To examine possible diluent and/or chair effects, a single subject (7AS) was given an iv injection of PEG200 alone (0.5 ml/kg). The procedure was conducted 26 days after this same animal received 3.5 mg/kg WR242511. Following PEG200 alone, this animal displayed hemoglobinuria at approximately 60 min postinjection. A second animal (F942) was placed in the restraint chair for ~60 min. No darkened urine was produced. A potential alternative solvent, Multisol, was identified. Multisol (48.5% water, 40% propylene glycol, 10% ethanol and 1.5% benzyl alcohol) is used as a solvent for preparing injectable drug solutions at USAMRICD and is the diluent for injectable diazepam. A single subject (16999) given an iv injection of Multisol (0.5 ml/kg) displayed no hemoglobinuria. Therefore, Multisol was selected as the new solvent for the preparation of WR242511. In addition to changing the solvent, the dose was increased from 3.5 mg/kg to 7.0 mg/kg, because very little MHb was produced at the lower dose. These changes were approved by the WR242511 Steering Committee.

Two subjects (P3C, female and JW0, male) were each administered WR242511 (7.0 mg/kg, in Multisol). Hemoglobinuria was observed in each animal. As presented in Table 4, very little MHb was produced, and JW0 died at ~36 hr postinjection. The attending veterinarian provided supportive treatment, and P3C survived. A full necropsy was performed on JW0. These results are presented in a subsequent section of this report. Additional hematological parameters, as well as blood chemistry results, are presented in Appendix F.

Table 4. Summary of initial iv administration of 7.0 mg/kg WR242511 in rhesus monkeys.

Animal	Maximum % MHb observed (time)	Outcome
P3C	1.3 (96 hr postinjection)	Sick, shock, survived (with intervention by veterinarian)
JW0	1.0 (6 hr postinjection)	Died ~36 hr postinjection

Several potential reasons for the outcome at 7.0 mg/kg were addressed by the WR242511 Steering Committee, and two additional tests were recommended. First, it was suggested that WR242511 be administered iv over an extended time (60 min). Second, it was suggested WR242511 be administered via the oral route. These additional studies are described below.

In a single male rhesus (F942), WR242511 (7.0 mg/kg, in Multisol) was administered iv, across 1 hr. For this iv injection, volume was 1.0 ml/kg. In this slow-infusion test, the animal was anesthetized (Telazol®), and WR242511 was administered iv using an infusion pump. A catheter was inserted to allow for urine sampling. No elevated MHb was observed, but hemoglobinuria was very apparent. Starting at 5 min postinjection, the urine became increasingly darker, and by 60 min postinjection, the urine sample was a very dark reddish brown with apparent sediment. Subsequent urine samples were clear. This animal did not appear sick and survived with no apparent ill effects. Additional hematological parameters, as well as blood chemistry results, are presented in Appendix F.

The final test in a rhesus monkey with WR242511 was to administer the drug orally. In this test, a WR242511-naïve male rhesus (6VY) was lightly anesthetized, and administered WR242511 (7.0 mg/kg, prepared in Multisol, in a volume of 2.0 ml/kg) via gastric intubation. No darkened urine was observed. This animal showed no appreciable MHb elevation (baseline: 0.5%, maximum MHb observed postinjection: 0.9%). Vomiting was observed at 24, 36 and 48 hr postinjection. The attending veterinarian monitored the animal, and noted nothing remarkable. The animal appeared alert, and aside from the vomiting, healthy. By 96 hr postinjection, the animal took a turn for the worse, and the attending veterinarian administered fluids. However, the animal died shortly thereafter (approximately 2 hr). A complete necropsy was performed (see below). This unexpected death was followed by solvent/procedure control test. Multisol alone was administered orally, under conditions identical to those present during the WR242511 oral exposure. No ill effects were noted in 16999 following Multisol alone. Additional hematological parameters, as well as blood chemistry results, are presented in Appendix F.

Table 5. Summary of effects of slow-infusion iv or oral administration of 7.0 mg/kg WR242511, or solvent control, in rhesus monkeys.

Animal	Route	Treatment	Dose	Outcome
F942	iv (slow)	WR242511	7.0 mg/kg	hemoglobinuria
6VY	per os	WR242511	7.0 mg/kg	hemoglobinuria, vomiting, died
16999	per os	Multisol	-	no ill effects

II.2.c. Pathology Reports

II.2.c.1. Clinical History

An adult, male rhesus monkey (JW0) was given two iv injections of WR242511 on two different occasions using two different solvents, PEG200 and Multisol (see Appendix B). Both administrations resulted in dark urine within one hr, and urinalysis confirmed the presence of hemoglobinuria. On day 1 after WR242511 (7.0 mg/kg) exposure, it was noted that the animal had vomited and had loose stools. Also, the animal appeared, lethargic, and was not eating. The animal was given supportive therapy, but died on day 2 postexposure. A complete necropsy was performed on 01 October 98.

A second adult, male rhesus monkey (6VY) received an oral treatment of WR242511 (7.0 mg/kg, prepared in Multisol, administered in volume of 2 ml/kg) via oral intubation. The animal vomited several times on days 2 and 3 postexposure. The animal was observed on the bottom of its cage on day 4 postexposure. Although supportive therapy was administered, the animal died several hr later. A complete necropsy was performed on 26 April 99. Urinalysis from a sample collected during postmortem examination revealed elevated protein and the presence of occult blood.

II.2.c.2. Necropsy results

Animal JW0 had no significant postmortem gross lesions. The carcass was in good flesh.

Animal 6VY was in good nutritional condition with ample subcutaneous and cavitary fat. There was a small amount of regurgitated food in the larynx. There were multiple organ ecchymoses and hemorrhages involving the epicardial surface of the heart, pericardium, internal thorax, and pancreas. The liver was diffusely dark red with a light-colored reticulated pattern that accentuates hepatic lobules (see Figure 3).

Copies of the original necropsy reports for animals JW0 and 6VY are presented in Appendix G.

II.2.c.3. Microscopic results

A. Animal JW0:

The lungs were diffusely and severely expanded by edema and fibrinous exudate (see Figure 2). Multifocally, several pulmonary arteries contained fibrin thrombi (see Figure 2). The liver exhibited diffuse, moderate hepatocellular degeneration, and congestion. There was mild, multifocal renal tubular epithelial degeneration and congestion. There was multifocal, mild, subacute myocarditis with a focal area of hemorrhage.

B. Animal 6VY:

The hepatic architecture was completely disrupted by sublobular necrosis and diffuse hemorrhage with moderate to severe periportal hepatocellular degeneration (see Figure 4). There was moderate to severe degeneration and necrosis of tubular renal epithelium, and, multifocally, tubules contain cellular, granular or hemoglobin casts (see Figure 5). The presence of intratubular hemoglobin was confirmed with special stains. There was diffuse, acute necrosis of the adrenal zona reticularis. There was mild, acute hemorrhage in the subendocardial and myocardial regions of the heart, accompanied by scattered myocardial degeneration. There was also multifocal, mild acute hemorrhage present in the periductular regions of the pancreas, meninges, pericardium, periesophageal fibroadipose tissue, and thymus. The hemorrhage in the pericardium was accompanied, multifocally, by intrarteriolar fibrin thrombi.

II.2.c.4. Comments

The histopathologic results strongly suggest that the lesions in the liver and kidney of both animals were the result of acute toxicity, although of varying degrees. The presence of hemorrhage in multiple organs from animal 6VY is compatible with a generalized coagulation disorder most likely secondary to severe liver dysfunction. Necrosis of the zona reticularis in the adrenal gland of animal 6VY is also consistent with an acute toxic insult. The presence of hemoglobin in urine and renal tubules indicates intravascular red blood cell damage (hemolysis). The exact mechanism of hemolysis is unknown. The pulmonary lesions in animal JWO reflect severe extravascular leakage of proteinaceous fluid and fibrin thrombosis. In light of the other lesions in these two animals, it is speculated that this too may be the result of a toxic effect on the pulmonary microvasculature. Although the acute myocardial hemorrhage appears to be related to the toxic events in both animals, the myocarditis is probably an older lesion. The different routes of administration (oral vs. intravenous) most likely explain the difference in target organs and severity of lesions in these two animals. The exact mechanism of toxic injury, whether an effect of the compound itself and/or a biotransformed metabolite, is uncertain.

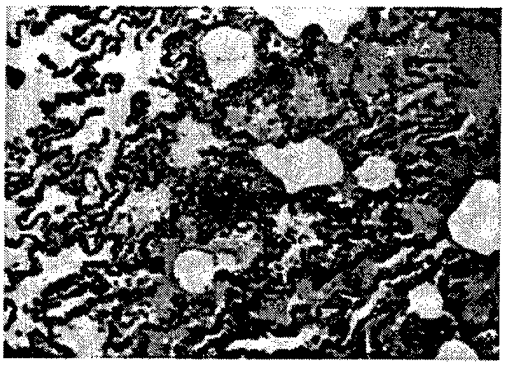

Figure 2. Lung with pulmonary edema and fibrin thrombus

Figure 3. Liver with diffuse congestion and reticular pattern.

Figure 4. Liver with submassive necrosis and hemorrhage.

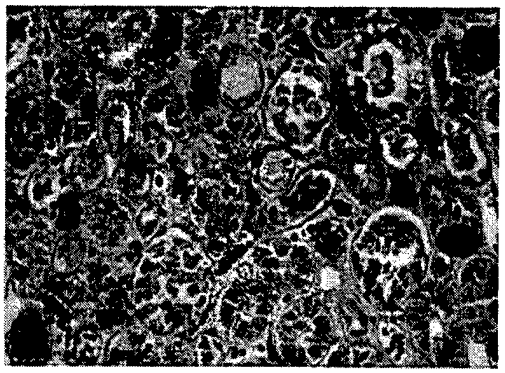

Figure 5. Kidney with degenerative and necrotic tubules.

II.2.d. Chemical Analysis

As a means of determining whether or not the observed effects on rhesus monkeys were due to a degraded or tainted sample, we provided several sample WR242511 solutions, as well as samples of the solvents, to the laboratory of Dr. Ming Shih, USAMRICD. She and her technician, Mr. J. Richard Smith performed mass spectrometry analyses on these samples. The results are provided below. In addition, to examine the possibility of pyrogen contamination, we sent sample WR242511 solutions, as well as samples of the solvents to the Celsis Laboratory Group. These results are also presented below.

II.2.d.1. Mass Spectrometry: Experimental

Solutions of WR242511 (ICD#1359) in Multisol were introduced to a mass spectrometer via a liquid stream consisting of a mixture of acetonitrile and water (90/10, v/v) delivered isocratically at 0.4 mL min^{-1} using a Hewlett Packard G1312A binary pump. The liquid stream was passed through a Hewlett Packard G1322A vacuum degasser prior to pump delivery. Samples were injected using flow injection analysis (FIA) with a Hewlett Packard G1313A automatic liquid sampler. The injection volume was 5 µL. Following FIA, the liquid stream was passed through a Hewlett Packard G1315A diode array detector (DAD) and then directed into a Hewlett Packard G1946A quadrupole mass spectrometer via an atmospheric pressure electrospray ionization (ESI) interface. UV absorbance was measured at 210 nm using a bandwidth of 4 nm with no reference wavelength used. The following MS conditions were used: positive ion full scan from *m/z* 70 to 600 resulting in a cycling time of 0.4 sec per cycle, fragmentor at 80 V, and capillary voltage at 4000 V. The drying gas was nitrogen introduced at a flow rate of 10 L min^{-1} and kept at 350 °C. Nitrogen was also used as the nebulization gas and maintained at a pressure of 40 psi.

II.2.d.2. Mass Spectrometry: Results

Electrospray ionization/mass spectrometry generally produces a $[M+H]^+$ protonated form of the molecular ion. The molecular weight of WR242511 without the DL tartarate salt is 373. The $[M+H]^+$ ion for WR242511 was readily observed at *m/z* 374 (see Figure 6). Small fragment ions of the parent compound were also observed at *m/z* 357 and 289. Their identification as fragment ions was confirmed by increasing the fragmentor voltage to induce greater fragmentation of the parent compound with a corresponding loss of the molecular ion. The solution was left out overnight (approximately 16 hr) at room temperature and exposed to air. No noticeable change in the mass spectrum was observed (see Figure 7). A fresh solution of WR242511 in Multisol was prepared and analyzed within 24 hr. The $[M+H]^+$ ion for WR242511 was once again readily observed at *m/z* 374 (see Figure 8). This solution was more dilute than the solution analyzed in Figure 5. As a result, ions from the Multisol solution were observed (see Figure 9). Analysis of the Multisol solution without WR242511 confirmed that the additional ions resulted from the Multisol. For additional information, see Appendix H.

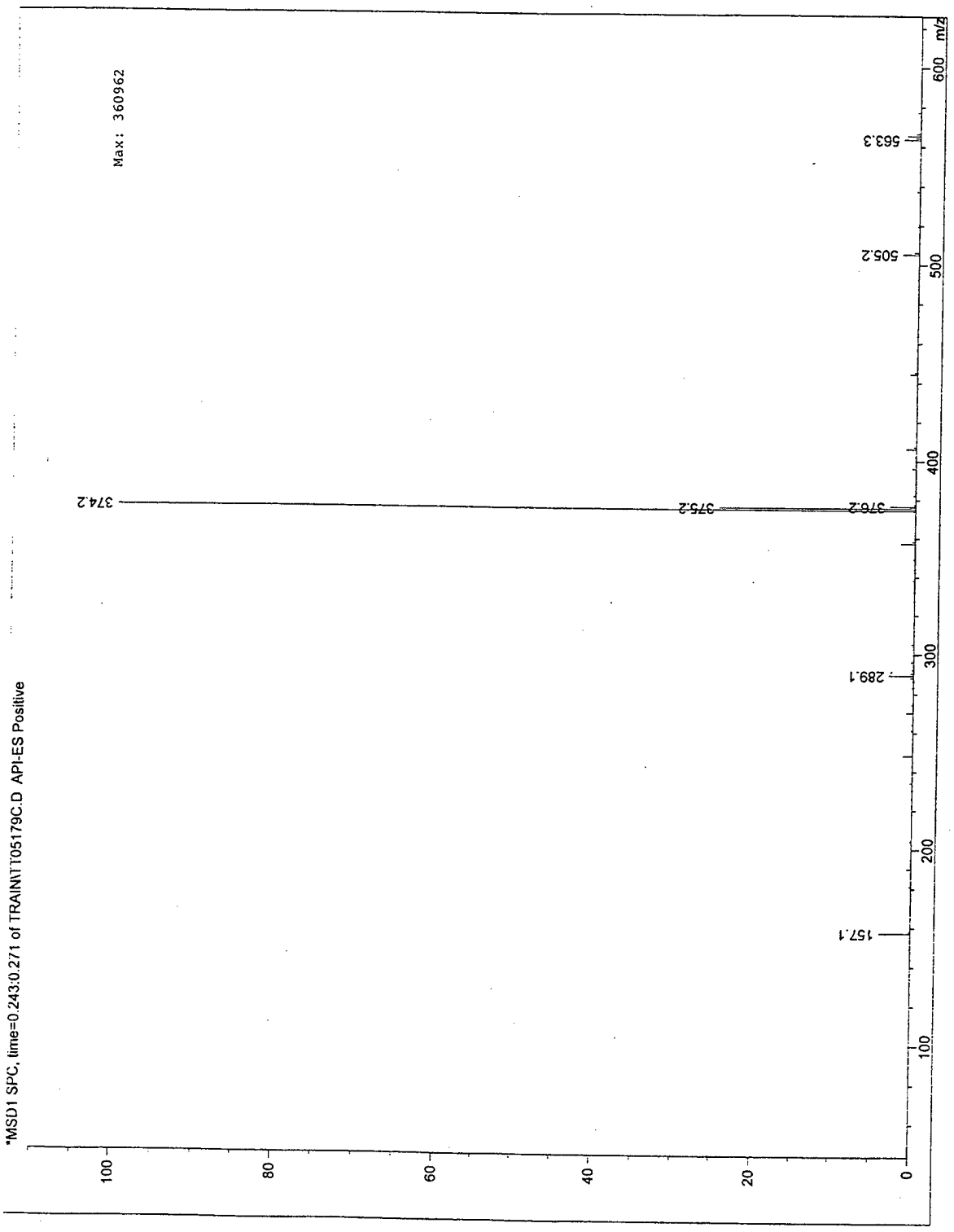

Figure 6. Mass spectrum of WR242511 (ICD # 1359) in Multisol (13.5 µg/ml^{-1}); prepared on 21 April 1999 and analyzed on 17 May 1999.

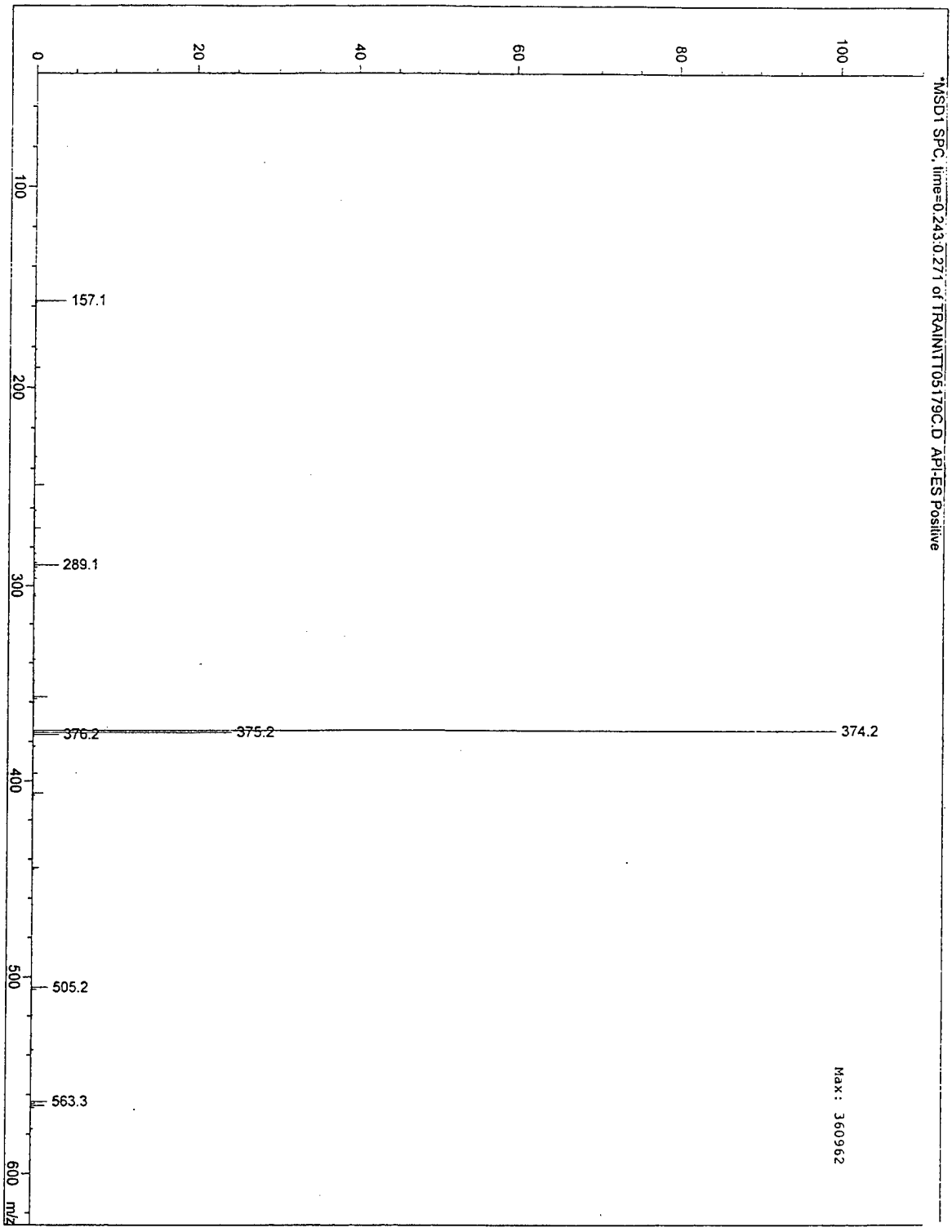

Figure 7. Mass spectrum of solution from Figure6 that was left open to air, at room temperature, for approximately 16 hours.

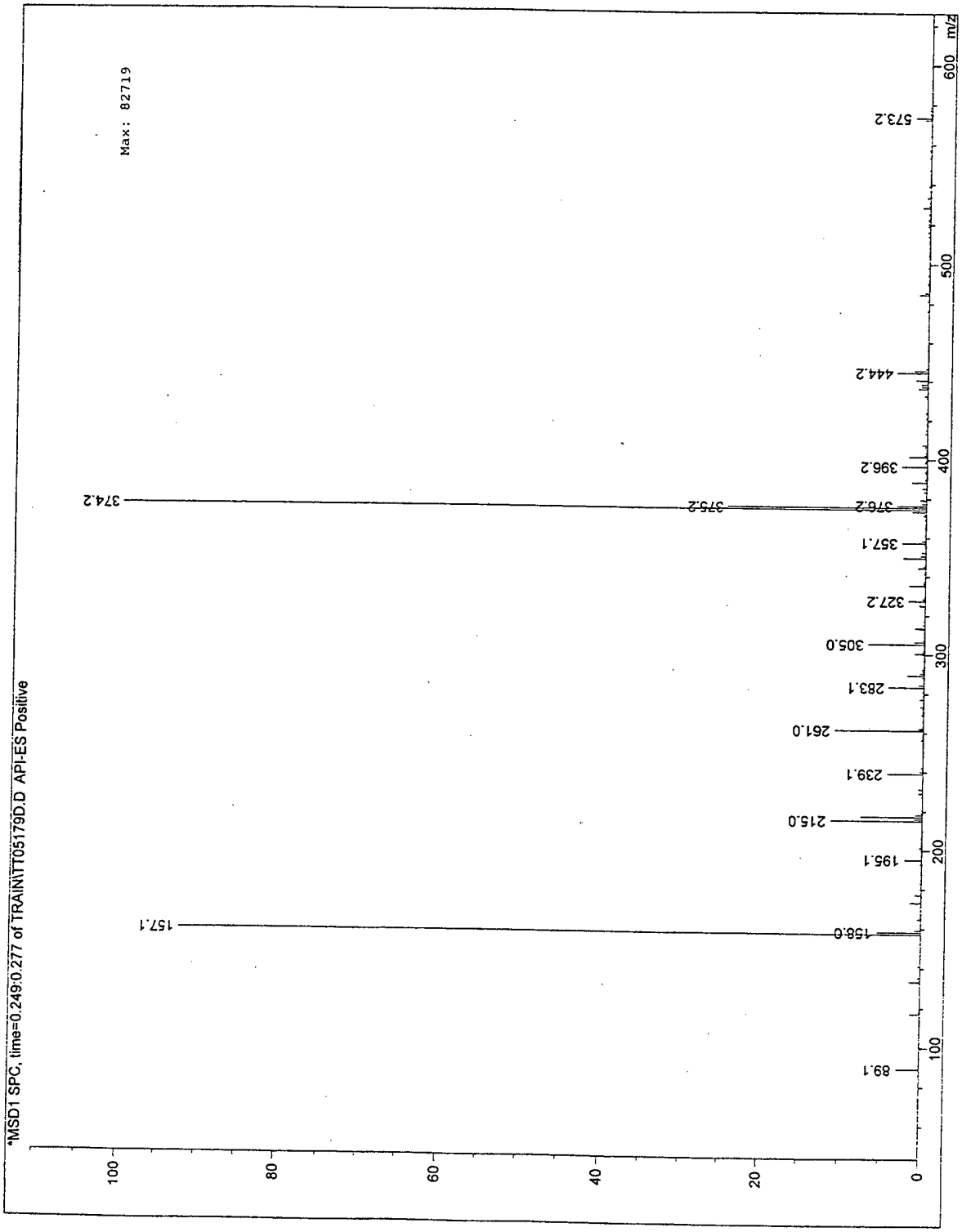

Figure 8. Mass spectrum of WR242511 (ICD # 1359) in Multisol (4.0 µg/ml^{-1}); prepared on 17 May 1999 and analyzed on 18 May 1999.

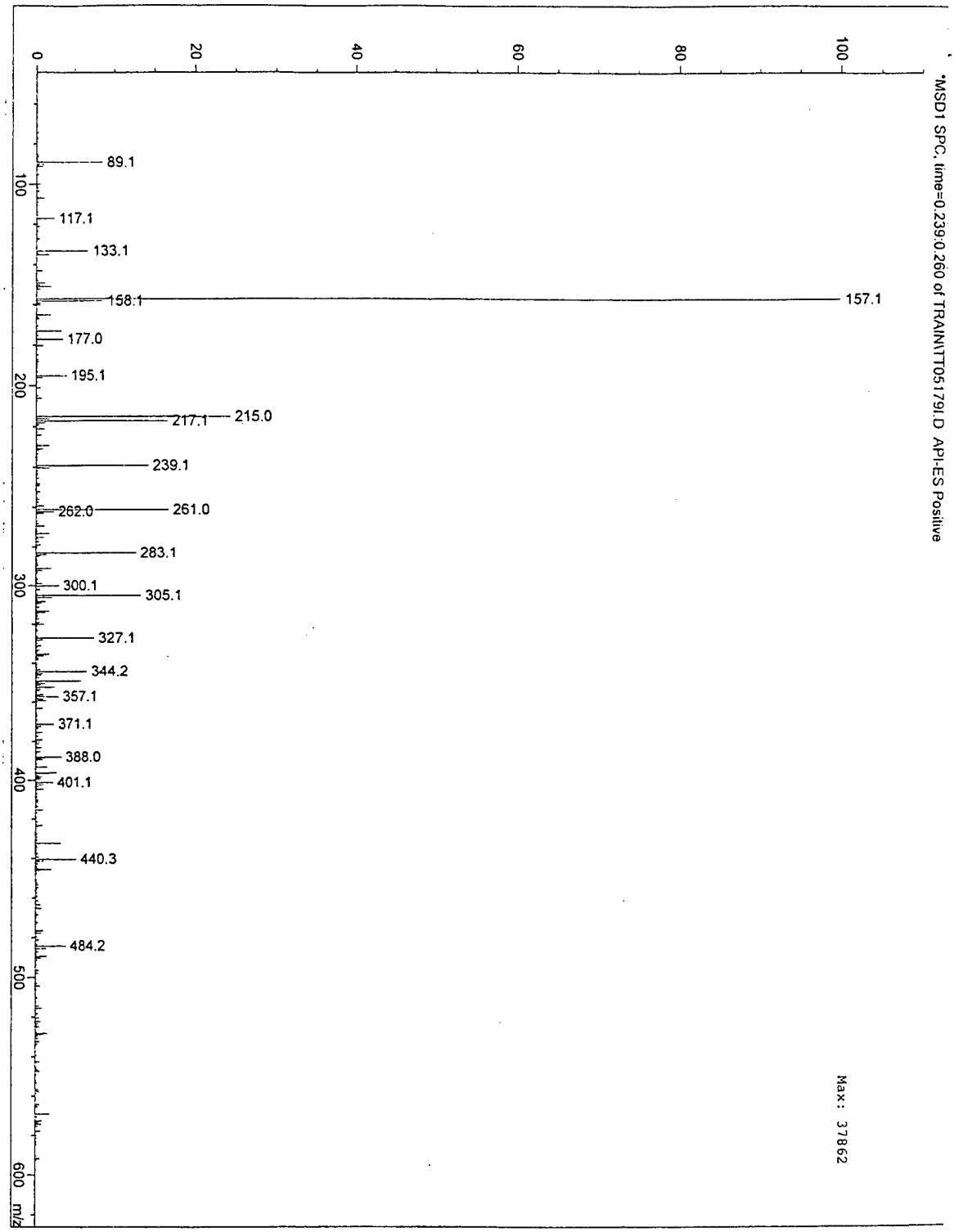

Figure 9. Mass spectrum of Multisol solution; prepared on 21 April 1999 and analyzed on 18 May 1999.

II.2.e. Pyrogen Testing

The results from these tests are presented in Appendix I. The samples appeared pyrogen-free, although very low pyrogen levels, below the threshold of detection, cannot be ruled out. It appears unlikely, however, that pyrogen contamination (in the drug or solvents) can explain the WR242511 results in the rhesus monkey, since similar types of toxicity have been seen in other species.

II.3. Discussion

Rhesus monkeys showed a typical elevation in blood MHb levels in response to iv injections of the prototypic MHb former $NaNO_2$ (Segment A). However, the experimental compound, WR242511, a potent MHb former in dogs, produce little or no elevation of MHb levels in rhesus monkeys (Segment B). Furthermore, toxicity was observed in the rhesus monkey exposed to WR242511, ranging from hemoglobinuria to liver damage, with death resulting in the most severely affected animals. Oxyhemoglobin levels also decreased following WR242511; cyanosis, however, was not apparent. Although sample sizes were small, we explored several possible reasons for these findings in the rhesus monkey exposed to WR242511.

1) SOLVENT
We examined the original solvent, PEG200. When WR242511 (3.5 mg/kg, iv) was first administered, with PEG200 as the solvent, hemoglobinuria was observed. Because hemoglobinuria was also observed in a single rhesus that received PEG200 alone, this solvent was replaced with Multisol. Multisol, alone, did not result in hemoglobinuria. However, when WR242511, prepared with Multisol, was administered, hemoglobinuria resulted. It is possible that the hemoglobinuria that was observed following PEG200 alone was, in fact, not due to the solvent. Rather, that particular animal had received 3.5 mg/kg WR242511 approximately 26 days prior to the PEG200 alone exposure. It is possible that WR242511 from the original exposure remained sequestered in the animal. When PEG200 alone was administered to this animal 26 days later, the sequestered drug was disturbed and produced the observed hemoglobinuria.

2) CHAIRING PROCEDURE
Chairing a rhesus monkey for 1 hr (or slightly longer) was also examined as a possible explanation for the hemoglobinuria. This, however, was ruled out.

3) RATE OF IV INJECTION
WR242511 was initially administered iv across 2-3 min. To address concerns about the total injection time, a slow-infusion (1 hr) test was performed. The animal survived, but did exhibit hemoglobinuria.

4) ROUTE OF ADMINISTRATION
WR242511 was initially administered iv in rhesus monkeys. All animals exhibited hemoglobinuria. One animal, which received 7.0 mg/kg, died, and a second animal which received this dose became ill, but recovered. When a single rhesus monkey was

orally dosed with 7.0 mg/kg WR242511, the animal died. It is noteworthy that in the beagle dog treated with WR242511 at the same doses used in the present study, the iv and per os routes of administration yielded similar patterns of methemoglobinemia (Noker, 1994).

5) DOSE

The doses used in this study are consistent with doses used previously in the beagle dog to produce MHb levels within the target range (Noker, 1994).

6) DRUG LOT AND CHEMICAL PURITY

The bottle number of WR242511 used in the present study with rhesus monkey is identical to that used by Noker (1994). Furthermore, to date, all analyses suggest that the test article was analytically pure and pyrogen-free.

7) SPECIES

Based on information currently available, the rhesus monkey appears to have been appropriate for this study. The rhesus monkey showed consistent MHb elevation following exposure to $NaNO_2$ (Segment A). Older data show that several 8-aminoquinolines produced elevated MHb in rhesus monkeys (Blanchard and Schmidt, 1946; Moe et al., 1949). Furthermore, levels of enzymes important for species-sensitivity and responsiveness to MHb-forming drugs, such as glucose-6-phosphate dehydrogenase and methemoglobin reductase are similar in the rhesus monkey and in humans (Eng, 1962; Rockwood et al., 2000).

The toxicity observed in the rhesus monkey following WR242511 does not appear to be unique to this species. Levine et al. (1996) reported a pattern of toxicity in rats and dogs following oral WR242511. However, three pieces of evidence in the beagle dog demonstrate toxicity particularly similar to that described in the rhesus monkeys.

> (1) In the final report by Dr. Patricia Noker entitled "Single dose iv and oral pharmacokinetics, bioavailability and metabolism study of WR242511 in dogs" (1994), hematuria was noted for the first day after drug administration in all dogs that received iv 7.0 mg/kg WR242511 (prepared in PEG200).
>
> (2) In a study summarized in a US Army-funded final report entitled, "Effects of methemoglobin versus potassium cyanide intoxication," by Dr. William D. Johnson (1987), one of two dogs died after receiving oral (gelatin capsules) WR242511 at 7.024 mg/kg once daily for four consecutive days. Unfortunately, a necropsy was not performed, and cause of death was not determined. It is unlikely, however, that methemoglobinemia precipitated the death, since MHb levels had started to decline (i.e., MHb levels were 32% and 29% three and two days prior to death, respectively). At specific times following the last day of drug administration, both animals receiving the multiple dosing regimen of WR242511 described above exhibited decreased activity (days 2-9), anorexia (days 2-9), diarrhea (days 3-4), and no stools (days 5-9). Furthermore, in the animal that died, considerable increases were observed in alanine aminotransferase (ALT),

aspartate aminotransferase (AST) and alkaline phosphatase (SAP) at 72 hr, 5 and 12 days after WR242511 administration, compared with baseline. These likely correspond to "hepatic cellular degeneration, skeletal and cardiac degeneration and/or obstructive icterus in dogs for ALT, AST and/or SAP, respectively. These increases were most likely a direct result of WR 242,511 administration" (p. 33). Other dogs reported in this study received a single oral dose of WR242511 at 7.024 or 14.048 mg/kg (two dogs per dose). One subject that received 14.048 mg/kg showed similar changes in ALT, AST and SAP at 72 hr after drug administration. No other significant changes were noted in these other animals, aside from time-dependent increases in MHb levels. Johnson (1987) concluded that, "Although WR242511 is a potent methemoglobin inducer, its associated toxicity, at least at the dose levels used in this study, would preclude its use as a cyanide antidote." (p. 42)

(3) In an open literature paper entitled, "Pharmacokinetics and kinetic-dynamic modeling of an 8-aminoquinoline candidate anticyanide and antimalarial drug (WR242511)," Marino et al. (1994) stated that all (beagle) dogs that received either iv (3.5 or 7.0 mg/kg, prepared in PEG200) or oral (7.0 mg/kg, gelatin capsules) WR242511 showed hemolysis, which cleared within 48 hr; however, gross hemoglobinuria was not observed. In addition, one animal vomited after receiving an oral dose of 7.0 mg/kg.

To date, data suggest that WR242511 is toxic across species and route of administration. Unless the anti-CN characteristics of this compound can be successfully dissociated from those that produce undesirable toxicity, WR242511 should not be pursued as a pretreatment for CN poisoning.

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Appendix A. List of Project Participants

List of participants (all participants affiliated with USAMRICD, APG-EA, MD, unless otherwise indicated)

NAME	DIVISION	CONTRIBUTION
Dr. Gary A. Rockwood	Drug Assessment	PI
Dr. Steven I. Baskin	Pharmacology	Collaborator
MAJ(P) Mark B. Gold	Comparative Medicine	Collaborator, Veterinary support
MAJ Kevin R. Armstrong	Comparative Medicine	Veterinary support
MAJ Crystal M. Briscoe	Comparative Medicine	Pathology support
MAJ Steven M. Duniho	Comparative Medicine	Pathology support
Dr. Ming L. Shih	Pharmacology	Chemical analysis support
J. Richard Smith	Pharmacology	Chemical analysis support
Steven Tucker	Comparative Medicine	Clinical chemistry
Anita V. Moran	Drug Assessment	Technician support
David W. Kahler	Drug Assessment	Technician support
Kenneth Mills	Comparative Medicine	Technician support
SGT Elton J. Machholz	Comparative Medicine	Veterinary technician support
SGT Matthew L. Jepsen	Comparative Medicine	Veterinary technician support
SGT Jason McKain	Comparative Medicine	Veterinary technician support

NAME	AFFILIATION	CONTRIBUTION
Dr. Robert Christenson	University of Maryland Clinical Chemistry Lab	Clinical chemistry (hemoglobinuria determination)

Appendix B. Timeline

Protocol 759 Timeline

1 April 1998

USAMRICD protocol approved: Safety and Behavioral Efficacy of a Methemoglobin Former in Nonhuman Primates Trained on the Serial Probe Recognition Task.
Protocol 1-05-98-000-A-759 (referred to as Protocol 759)
PI: G. A. Rockwood

13 May 1998

Sodium nitrite (19.0 mg/kg, iv) administered to an anesthetized male (16999, Byron).

14 May 1998

Sodium nitrite (16.0 mg/kg, iv) administered to an anesthetized female (B055, Nancy).

27 May 1998

Sodium nitrite (19.2 mg/kg, iv) administered to an anesthetized male (7AS, Astin).

10 June 1998

Sodium nitrite (19.4 mg/kg, iv) administered to an anesthetized male (JWO, Joe).

11 June 1998

Sodium nitrite (20/mg/kg, iv) administered to an anesthetized male (F942, Kong).

16 June 1998

Sodium nitrite (19.6 mg/kg, iv) administered to an anesthetized female (P3C, Sheba).

13 August 1998

WR242511 (3.5 mg/kg, iv, in PEG200) administered to P3C.

19 August 1998

WR242511 (3.5 mg/kg, iv, in PEG200) administered to 7AS.

20 August 1998

WR242511 (3.5 mg/kg, iv, in PEG200) administered to B055.

1 September 1998

WR242511 (3.14 mg/kg [due to catheter clog], iv, in PEG200) administered to JW0.
WR242511 (3.5 mg/kg, iv, in PEG200) administered to F942.

3 September 1998

WR242511 (3.5 mg/kg, iv, in PEG200) administered to 16999.

14 September 1998

PEG200 (iv) administered to 7AS.

15 September 1998

Chair only, no injection (F942).

24 September 1998

Administered new potential solvent, Multisol (iv) to 16999.

29 September 1998

WR242511 (7.0 mg/kg, iv, in Multisol) administered to JW0
WR242511 (7.0 mg/kg, iv, in Multisol) administered to P3C.

1 October 1998

JW0 found dead in cage. Necropsy performed.
P3C observed in home cage – pale, labored breathing, in distress. Intervention by attending veterinarian. P3C survived.

29-31 October 1998

Pyrogen testing on WR242511, PEG200 and Multisol samples, by Celsis Laboratory Group.

30 October 1998

Steering Committee meeting at USAMMDA. Slow iv infusion, and/or oral administration recommended.

10 December 1998

Steering Committee meeting USAMMDA. Protocol 759 addenda presented: slow infusion (7.0 mg/kg, iv, in Multisol, administered across 1 hr) and oral administration (7.0 mg/kg, per os, in Multisol),

13 January 1999

WR242511 (7.0 mg/kg, iv, in Multisol) administered to F942 (anesthetized), using slow infusion (1 hr).

16 February 1999

Steering Committee meeting at USAMMDA and ICD (videoconference). Slow infusion study summary presented.
Recommendation: oral dosing, in a single WR242511-naïve rhesus.

24 February 1999

Drs Rockwood and Baskin from USAMRICD met with Dr. Heiffer and MAJ Bonner at WRAIR to discuss details for oral dosing. It was agreed upon to expose a single, WR242511-naïve male rhesus to 7.0 mg/kg, per os, in Multisol.

21 April 1999

WR242511 (7.0 mg/kg, per os, in Multisol) administered to a WR242511-naive male rhesus (6VY, Adams). Procedure performed with animal under light anesthesia.

25 April 1999

6VY found dead in cage.

26 April 1999

Necropsy performed on 6VY.

3 May 1999

Multisol (per os) administered to 16999. Procedure performed with animal under light anesthesia.

17-18 May 1999

Mass spectrometry analyses conducted at USAMRICD on WR242511 solutions and on Multisol

19 May 1999

Steering Committee meeting at USAMMDA. Oral WR242511 study summary presented, including pathology results.

Appendix C. Test Articles

Test Articles

Sodium Nitrite	Source:	Sigma
WR242511-AE (ICD # 1359)	Source:	Walter Reed Army Institute of Research (WRAIR)
	Quantity:	~10 g
	Bottle No.:	BM05816
	Manuf. Code:	DJD-08-235
	Date received at USAMRICD:	May 1998
PEG200	Source:	Sigma
	Components:	Polyethylene glycol
Multisol	Source:	Prepared in-house
	Components:	Water: 48.5%
		Propylene glycol: 40.0%
		Ethanol: 10.0%
		Benzyl alcohol: 1.5%

Appendix D. Animal Histories

Sheba, RH P3C Female Rhesus

Drug Procedure History Medical History,

28FEB95 to 30 APR 98 Ketamine / Xylazine IM Anesthesia For TB test /Physical Exams (X 13)
28APR95 Ivermectin PO for Intestinal Parasites
28 JUN95 to 30JUN95 Buprenorphine IM for Pain due to abscess
28JUN95 to 7JUL95 Cephazolin PO Antibiotic for abscess
24JUL95 Ketamine / Xylazine IM Anesthesia for **IRRADIATION** Total Dose 700 rads whole body
24JUL95 to 6AUG95 "SC" compound SQ QID
31JUL95 to 6AUG95 Rocephin 250 mg IV QID
31JUL95 to 6AUG95 Gentocin 10 mg SQ QID
7AUG95 to 18AUG95 Tintin 125 mg SQ BID
19SEP95 to 25SEP95 Flagyl PO for Giardia
18DEC97 Ketamine anesthesia IM, **Kidney Transplant Donor** Cepha/Torbogesic IM TID x 2 days
18MAY98 to 30AUG99 Telazol 3 mg/kg IM Anesthesia Physical exams TB test
16JUN98 Telazol/Isoflurane Anesthesia 19.2 mg/kg **$NaNO_2$ IV**
13AUG98 **WR242511 3.5 mg/kg** IV
29SEP98 **WR242511 7.0 mg/kg** IV

Nancy RH 90B055 Female Rhesus

Drug Procedure History Medical History,

23SEP91 to 30 AUG99 Telazol or Ketamine IM Anesthesia for Physical Exam, TB test, blood (X 47)
9DEC91 Ivermectin PO Whip worms
11MAY92 Telazol Anesthesia, **SEB Toxoid Exposure**
11JUN92 Telazol Anesthesia (blood for SEB antibodies)
16JUN92 Telazol Anesthesia **SEB Exposure Aerosolized**
2SEP92 to 21SEP95 Telazol anesthesia **Trachobronchial Lavage (X 5)**
23MAY93 to 29MAY93 Bactrium PO SID
24MAY93 Telazol anesthesia Telemetry **Unit implant**
18JUL95 Telazol anesthesia **Anthrax Exposure**
31AUG95 Telazol anesthesia **Anthrax Exposure**
2SEP95 to 7SEP95 Telazol anesthesia **Blood Cultures**
14MAY98 Telazol/Isoflurane Anesthesia **Exposure 16.0 mg/kg NaNO2 IV**
20AUG98 Exposure **WR242511 3.5 mg/kg IV**

Byron RH16999 Male Rhesus

Drug Procedure History Medical History,

10SEP93 to 21SEP99 Telazol or Ketamine IM Anesthesia PE, TB test, Blood (X 45)
27DEC93 to 5FEB94 Telazol or Ketamine **Exposure to unknown experimental substance**
18MAY94 Telazol anesthesia Plethygmograpgy, **Exposure SEB Aerosol exposure (5 LD_{50})**
18JUL95 Telazol anesthesia **Vaccinated Anthrax**
24AUG95 Telazol anesthesia **Tracheobroncho Lavage**
30AUG95 Telazol anesthesia **Exposure Anthrax**
14MAY96 to 17MAY96 Telazol anesthesia **ID Exposure to unknown substance**
13MAY98 Telazol/Isoflurane anesthesia **Exposure 19.0 mg/kg $NaNO_2$ IV**
3SEP98 **Exposure WR242511 3.5 mg/kg IV**
24SEP98 **Exposure Multisol IV**
3MAY99 **Exposure Multisol Oral**

Kong RHF942Male Rhesus

Drug Procedure History Medical History,

9NOV87 to 3NOV98 Ketamine or Telazol Anesthesia for PE, TB test, Blood (X 37)
22NOV87 to 23NOV87 Polyflex IM
24NOV87 to 27JAN88 Tilamin 100 mg PO SID
3MAY88 to 29JUN88 Ketamine Biotal PE, Blood, TB test (X 9)
3MAY88 Ketamine/Biotal Anesthesia **"BM" Aspertate Exposure, Irradiation (unk dose)**
6JUN88 to 11JUN88 **Exposure 0.5 ml "GF" SQ**
29MAY to 6JUN88 **Exposure 0.5 ml "GF" SQ**
31JUL92 to 13AUG92 3.5 ml Bactrin PO BID
14SEP92 Acepromazine, Meperidine, Narcan
1JAN94 **POSITIVE HERPES (Ocular)**
14SEP95 Ketamine anesthesia Endoscopy
11JUN98 Telazol/Isoflurane anesthesia **Exposure 20 mg/kg $NaNO_2$ IV**
1SEP98 Exposure **3.5 mg/kg WR 242511 IV**
7JAN98 Exposure **Telazol Only MHb**
13JAN98 Exposure **WR242511 7.0 mg/kg IV SLOW (60 minutes)**

JOE RHJW0 Male Rhesus

Drug Procedure History Medical History,

31MAR94 to 28AUG98 Ketamine or Telazol anesthesia for PE, TB test, Blood (X 28)
29AUG94 Ketamine anesthesia **Exposure "MDGFASC"**
30AUG94 to 7 SEP94 **Exposure "WO" SQ SID**
1SEP94 Ketamine/Xylazine **Bone Marrow Aspiration**
31OCT94 to 1NOV94 **Exposure 2 ml "BM" Aspirate**
11DEC95 Flagyl PO Intestinal Parasites
11DEC95 to 18DEC95 125 mg Metrandazol PO Fecal Bacteria
10JUN98 Telazol/Isoflurane anesthesia **Exposure NaNO2 IV 19.4 mg/kg**
1SEP98 **Exposure WR242511 3.5 mg/kg IV**
29SEP98 **Exposure WR 242511 7.0 mg/kg IV** (Died)

ASTIN RH7AS Male Rhesus

Drug Procedure History Medical History,

18AUG89 to 21SEP99 Ketamine or Telazol anesthesia for PE, TB test, Blood (X 49)
27MAY98 **Exposure 19.2 mg/kg NaNO2 IV**
19AUG98 **Exposure WR242511 3.5 mg/kg IV**
14SEP98 **Exposure PEG 200 IV**

ADAMS RH6VY Male Rhesus

Drug Procedure History Medical History,

17AUG89 to 23MAR99 Ketamine or Telazol anesthesia for PE, TB test, Blood
10MAR98 Ketamine/Acepromazine anesthesia **Exposed to 3.3 mg Physostimine IV**
8JUN98 Ketamine/Acepromazine anesthesia **Exposed to 3.3 mg Physostimine IV**
31AUG98 Ketamine/Acepromazine anesthesia **Exposed to 3.3 mg Physostimine IV**
15SEP98 Ketamine/Acepromazine anesthesia **Exposed to 3.3 mg Physostimine IV**
17NOV98 Ketamine/Acepromazine anesthesia **Exposed to 3.3 mg Physostimine IV**
02MAR99 Ketamine/Acepromazine anesthesia **Exposed to 3.3 mg Physostimine IV**
21APR99 Telazol anesthesia Exposed to WR242511 7.0 mg/kg Orally
25APR99 Deceased

Appendix E. Hematologic Data ($NaNO_2$)

ASTIN RH7AS Male Rhesus

Methemoglobin Sampling Table 27MAY98 $NaNO_2$

Time	OSM3 min. from inj	$NaNO_2$ Dose MG/KG	Sam. #	OSM3 1 (no print)				OSM3 2 (Print)			
				THb	HbO_2	HbCO	MHb	THb	HbO_2	HbCO	MHb
11:40	0	0	1643	11.5	99.2	-0.2	0.4	11.0	99.3	-0.9	0.7
			1644	11.3	99.2	-0.1	0.3	11.3	99.1	-0.9	0.8
12:01	6	4.0	1645	11.0	97	-0.1	2.5	10.9	96.9	-0.8	2.9
12:06	11	4.0	1646	10.8	96.9	-0.2	2.6	10.7	97	-1.0	2.9
12:10	18	4.0	1647	10.6	96.1	-0.4	3.6	10.7	96.3	-0.8	3.6
			1648	11.0	96.2	-0.4	3.4	10.6	96.3	-0.9	3.6
			1649	10.9	96.3	-0.4	3.4	10.7	96.3	-0.9	3.6
12:37	13	7.0	1650	10.5	93.9	-0.5	5.8	10.1	94	-0.9	5.9
			1651	10.5	93.9	-0.6	5.8	10.3	93.8	-1.1	6.2
			1652	10.4	94.0	-0.5	5.7	10.3	93.9	-1.1	6.0
1302	16	10.0	1653	9.0	92.1	-0.7	7.7	8.9	91.9	-1.3	8.1
			1654	9.0	92.1	-0.7	7.7	9.0	92.1	-1.2	7.9
			1655	9.0	92.2	-0.7	7.6	9.0	92.3	-1.1	7.7
13:27	15	12.4	1656	9.2	91.1	-0.7	8.6	9.2	91.5	-1.2	8.6
			1657	9.3	91.4	-0.7	8.4	9.2	91.6	-1.2	8.5
			1658	9.4	91.5	-0.6	8.3	9.2	91.6	-1.1	8.4
1347	7	15.6	1659					9.5	90.2	-1.1	9.8
		Post	1660	9.5	89.9	-0.7	9.8	9.4	90.1	-1.2	9.9
		Arrest	1661	9.5	90.1	-0.7	9.6	9.7	90.1	-1.2	9.8
14:03	26	15.6	1662	9.4	89.2	-0.6	10.4	9.3	89.3	-1.1	10.7
			1663	9.3	89.3	-0.8	10.4	9.4	89.4	-1.2	10.6
			1664	9.2	89.5	-0.6	10.2	9.3	89.6	-1.1	10.4
14:28	13	17.4	1665	8.9	89.3	-0.5	10.4	9.0	89.2	-1.2	10.8
			1666	8.9	89.4	-0.7	10.4	9.1	89.5	1.3	10.6
			1667	9.0	89.4	0.7	10.3	9.3	89.4	-1.4	10.7
14:52	14	19.2	1668	9.1	89.8	-0.5	9.9	9.0	89.8	-1.1	10.3
			1669	9.3	89.6	-0.8	10.2	9.1	89.9	-1.0	10.1
			1670	9.1	89.8	-0.6	10.0	9.1	89.9	-1.3	10.2
15:01	17	19.2	1671	9.3	89.7	-0.7	10.0	9.0	89.9	-1.1	10.2

Byron RH16999 Male Rhesus

Methemoglobin Sample Table 13MAY98 $NaNO_2$

Time	Time from inj	$NaNO_2$ Dose mg/kg	Sam. #	OSM3 1 (no print)				OSM3 2 (Print)			
				THb	HbO_2	HbCO	MHb	THb	HbO_2	HbCO	MHb
12:15	0	0	1608	11.1	99.3	-0.3	0.4	11.1	99.2	-0.7	0.6
			1609	11.1	99.3	-0.3	0.4	11.0	99.4	-0.7	0.5
13:03	33	5.2	1610	10.3	95.9	-0.2	3.7	10.1	95.8	-0.8	4.1
			1611	10.2	95.9	-0.4	3.8	10.2	95.7	-1.0	4.2
13:22	15	7.8	1612	10.7	94.5	-0.3	5.1	10.4	94.4	-0.8	5.5
			1613	10.6	94.6	-0.4	5.1	10.5	94.4	-0.8	5.4
14:01	27	10.4	1614	10.3	87.8	-0.4	7.6	10.0	88.1	-0.8	7.7
			1615	10.2	87.9	-0.3	7.4	9.8	87.6	-0.8	7.9
14:28	18	13.0	1616	10.0	85.6	-0.4	9.7	9.8	85.8	-0.8	10.0
			1617	10.0	85.4	-0.3	9.6	9.9	85.8	-0.8	10.1
14:50	17	16.0	1618	10.1	82.5	-0.4	12.2	9.8	82.3	-0.8	12.6
			1619	10.0	82.4	-0.4	12.1	10.1	86.5	-1.5	12.1
			1620	10.1	82.2	-0.4	12.1	9.7	82.2	-0.7	12.5
			1621	10.0	82.0	-0.4	12.2	9.7	82.1	-0.9	12.6
15:06	12	19	1622	9.9	79.2	-0.3	14.7	9.8	79.5	-0.8	15.2
			1623	10.0	78.9	-0.3	15.0	9.8	78.9	-1.0	15.4
			1624	10.0	78.7	-0.4	15.0	9.8	78.8	-0.8	15.3

JOE RHJW0 Male Rhesus

Methemoglobin Sample Table 10JUN98 Exposure NaNO2 IV 19.4 mg/kg

Time	Time from inj	$NaNO_2$ Dose mg/kg	Sam. #	OSM3 1 (no print)				OSM3 2 (Print)			
				THb	HbO_2	HbCO	MHb	THb	HbO_2	HbCO	MHb
11:49	0	0	1674	9.6	99.1	-0.5	0.6	9.4	99.3	-1.0	0.6
			1675	9.6	99.2	-0.5	0.5	9.5	99.2	-1.1	0.8
			1676	9.5	99.3	-0.5	0.5	9.4	99.3	-1.1	0.8
12:13	13	4.2	1677	10.3	97.4	-0.2	2.3	10.1	97.4	-1.0	2.6
			1678	10.1	97.3	-0.4	2.4	9.9	97.6	-0.9	2.4
			1679	10.0	97.3	-0.4	2.3	9.9	97.3	-1.1	13.4
12:27	14	7.4	1680	9.9	97.0	-0.4	2.7	10.0	97.0	-1.0	3.0
			1681	9.8	97.1	-0.4	2.6	10.0	96.7	-1.1	3.2
12:45	24	7.4	1682	10.2	95.5	-0.4	4.2	10.1	95.3	-1.1	4.7
			1683	10.3	95.4	-0.4	4.3	10.1	95.2	-1.2	4.8
			1684	10.2	95.4	-0.4	4.3	10.2	95.3	-1.1	4.7
13:20	14	11.0	1685	9.9	93.6	-0.4	6.1	10.2	93.5	-1.1	6.5
			1686	10.1	93.8	-0.4	5.9	9.9	93.7	-1.3	6.3
			1687	10.2	93.8	-0.4	5.9	10.0	93.8	-1.2	6.3
13:51	14	14.6	1688	9.8	92.1	-0.3	7.6	9.7	91.8	-1.0	8.2
			1689	9.9	92.3	-0.3	7.4	9.7	92.0	-1.1	8.0
			1690	9.9	92.2	-0.4	7.5	9.8	91.8	-1.2	8.2
14:24	14	17.2	1691	9.3	90.54	-0.6	9.2	9.1	90.8	-1.3	9.3
			1692	9.5	90.8	-0.7	9.0	9.3	90.8	-1.1	9.2
			1693	9.6	90.8	-0.7	9.0	9.1	90.8	-1.2	9.2
14:52	14	19.4	1694	9.2	89.9	-0.7	9.9	9.1	90.0	-1.2	10.1
			1695	9.2	89.8	-1.0	10.1	9.2	90.1	-1.2	9.9
			1696	9.1	89.8	-1.0	9.9	9.1	90.3	-1.1	9.7
15:03	25	19.4	1697	9.1	90.1	-0.8	9.7	9.0	90.4	-0.8	9.5
			1698	9.2	90.2	-0.9	9.6	9.1	90.4	-1.2	9.7
			1699	9.0	90.3	-0.7	9.5	9.1	90.3	-1.3	9.7

Kong RHF942Male Rhesus

Methemoglobin Sample Table 11JUN98 Exposure 20 mg/kg $NaNO_2$ IV

Time	Time from inj	$NaNO_2$ Dose mg/kg	Sam. #	OSM3 1 (no print)				OSM3 2 (Print)			
				THb	HbO_2	HbCO	MHb	THb	HbO_2	HbCO	MHb
10:30	0	0	1703	12.5	99.1	-0.5	0.5	11.9	99.4	-1.0	0.6
			1704	12.4	99.1	-0.5	0.5	12.3	99.3	-1.1	0.8
			1705	12.4	99.2	-0.4	0.5	12.0	99.2	-1.1	0.8
11:02	10	5.2	1706	11.9	97.0	-0.4	2.6	11.8	97.1	-1.1	2.8
			1707	12.1	97.1	-0.4	2.5	11.9	97.3	-1.0	2.7
11:09	20	5.2	1708	11.8	96.1	-0.5	3.5	11.6	96.3	-1.1	3.6
			1709	11.4	96.3	-0.5	3.4	11.7	96.4	-1.0	3.5
			1710	11.6	96.1	-0.5	3.5	11.6	96.3	-1.1	3.6
11:44	19	7.2	1711	10.8	95.1	-0.6	4.6	10.9	95.4	-1.1	4.7
			1712	10.9	95.2	-0.6	4.5	10.7	95.4	-1.1	4.5
			1713	10.9	95.4	-0.5	4.3	10.8	95.3	-1.3	4.7
12:18	19	10.6	1714	10.8	94.0	-0.6	5.7	10.9	94.1	-1.3	6.0
			1715	11.1	94.0	-0.6	5.7	11.0	94.3	-1.2	5.8
			1716	10.8	94.1	-0.7	5.6	10.7	94.3	-1.1	5.7
12:48	19	14.6	1717	10.5	92.2	-0.7	7.5	10.5	92.2	-1.2	7.8
			1718	10.4	92.2	-0.6	7.5	10.5	92.4	-1.2	7.6
			1719	10.5	92.3	-0.7	7.4	10.5	92.6	-1.2	7.4
13:12	14	18.0	1720	10.0	90.8	-0.6	8.9	10.3	90.9	-1.1	9.0
			1721	10.3	91.0	-0.6	8.7	10.3	90.9	-1.1	9.0
			1722	10.4	91.0	-0.7	8.7	10.4	91.0	-1.2	8.9
13:46	19	20.0	1723	9.6	90.0	-0.8	9.9	9.7	89.8	-1.2	10.1
			1724	10.0	90.0	-0.8	9.9	9.6	90.0	-1.1	10.0
			1725	9.9	90.1	-0.8	9.7	9.9	90.0	-1.0	9.8

Nancy RH 90B055 Female Rhesus

Methemoglobin Sample Table 14MAY98 $NaNO_2$ IV

Time	Time from Inj	$NaNO_2$ Dose mg/kg	Sam. #	OSM3 1 (no print)				OSM3 2 (Print)			
				THb	HbO_2	HbCO	MHb	THb	HbO_2	HbCO	MHb
10:00	0	0	1626	11.1	99.4	-0.4	0.4	11.0	99.2	-0.9	0.8
			1627	11.2	99.2	-0.4	0.5	10.9	99.2	-0.9	0.8
10:13	2	4.0		10.5	95.4	0.1	3.9				
10:17	6	4.0					2.4				
10:21	10	4.0		10.6	96.7	-0.5	3.0				
10:33	25	4.0	1628	10.6	96.1	-0.5	3.7	10.5	95.8	-1.0	4.1
			1629	10.6	96.0	-0.5	3.7	10.4	96.0	-1.0	4.0
10:46	4	7.0			94.7	-0.7	5.2				
10:52	12	7.0	1630	10.3	93.4	-0.6	6.4	9.9	93.4	-0.9	6.5
			1631	10.1	93.5	-0.6	6.2	10.3	93.4	-1.1	13.4
11:10	8	10.0	1632	10.0	90.6	-0.6	9.2	10.0	90.5	-1.2	9.6
			1633	10.1	90.7	-0.7	9.1	10.0	90.6	-1.1	9.3
			1634					10.1	90.6	-1.1	9.3
11:35	13	11.6	1635	9.8	87.9	-1.0	12.1	10.0	87.8	-1.4	12.3
			1636	10.0	88.0	-1.0	11.9	9.9	87.9	-1.3	12.1
12:02	18	13.0	1637	9.8	86.8	-1.2	13.3	9.9	86.8	-1.3	13.3
			1638	10.0	86.8	-1.1	13.1	9.7	86.8	-1.3	13.2
12:28	19	16.0	1639	9.9	84.7	-1.1	15.3	9.9	84.5	-1.4	15.6
			1640	9.8	84.7	-1.2	15.4	9.7	84.6	-1.5	15.5

Sheba, RH P3C Female Rhesus

Methemoglobin Sample Table 16JUN98 $NaNO_2$

Time	Time from inj	$NaNO_2$ Dose mg/kg	Sam. #	OSM3 1 (no print)				OSM3 2 (Print)			
				THb	HbO_2	HbCO	MHb	THb	HbO_2	HbCO	MHb
11:04	0	0	1728	11.8	99.0	-0.4	0.4	11.6	99.1	-1.1	0.6
			1729	12.0	98.9	-0.4	0.5	11.6	99.0	-1.1	0.7
			1730	11.7	98.8	-0.4	0.6	11.8	98.9	-1.1	0.7
11:32	20	4.4	1731	10.8	93.9	-0.5	2.9	10.9	94.0	-0.9	2.9
			1732	10.7	94.0	-0.3	2.8	10.6	94.1	-0.8	2.8
			1733	10.9	93.8	-0.5	2.9	10.5	93.9	-1.0	3.1
12:00	21	8.4	1734	10.5	91.0	-0.4	5.7	10.7	90.8	-0.9	6.0
			1735	10.8	91.0	-0.4	5.6	10.7	91.0	-0.9	5.8
			1736	10.9	90.8	-0.4	5.7	10.6	90.9	-1.1	5.9
13:34	19	11.2	1737	10.3	90.7	-0.6	6.6	10.6	90.6	-1.0	6.7
			1738	10.7	91.0	-0.5	6.4	10.4	91.1	-1.0	6.5
			1739	10.6	90.8	-0.5	6.5	10.4	90.9	-1.2	6.8
13:04	18	14.8	1740	9.6	91.2	-0.7	7.6	9.3	91.5	-1.1	7.5
			1741	9.7	91.5	-0.6	7.3	9.3	91.5	-1.2	7.6
			1742	9.7	91.4	-0.5	7.4	9.4	91.5	-1.2	7.6
13:35	18	18.4	1743	9.8	90.1	-0.7	8.5	10.0	89.9	-1.2	8.8
			1744	10.0	90.2	-0.6	8.4	9.9	89.9	-1.4	8.9
			1745	9.8	90.0	-0.8	8.6	9.9	90.0	-1.3	8.8
14:08	18	19.6	1746	10.7	90.3	-0.7	7.7	10.7	89.8	-1.1	7.9
			1747	11.1	90.3	-0.6	7.5	10.7	90.3	-1.2	7.7
			1748	10.8	90.4	-0.6	7.4	10.8	90.3	-1.0	7.5

Appendix F. Hematologic and Blood Chemistry Data (WR242511)

ADAMS RH6VY Male Rhesus

Adams RH6VY WR242511 7.0 mg/kg PO
21APR99

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK		SGPT	Na	K	Cl
Base	6.15	46.7	15.3	5.65	24.8	32.6	71	11.7	5.2	228		16	159	4.6	119
+1h	6.17	46.7	15.2	7.77	24.6	32.5	69	11.1	0.8	618		16	161	3.6	124
+6h	6.33	48.4	16.0	10.6	25.2	33.0	116	18.4	5.8	889		29	153	3.5	109
+24h	6.21	47.5	15.6	11.0	25.0	32.8	120	16.8	5.0	302		36	150	3.5	110
+48h	6.36	48.9	15.7	6.74	24.7	32.2									

ADAMS RH6VY Male Rhesus

Methemoglobin Sample Table
21APR99

Time	Time from inj	Sam. #	OSM3 A					OSM3 B					
			THb	HbO_2	HbCO	MHb	O_2ct	Sample	THb	HbO_2	HbCO	MHb	O_2ct
21APR99	Base	5532	15.2	49.4	0.0	0.4	10.4	1985	15.4	51.3	-0.7	0.6	11.0
		5533	15.1	49.8	-0.1	0.6	10.5	1986	15.3	51.4	-0.8	0.6	10.9
	+1h	5534	15.2	34.3	0.1	0.5	7.2	1987	15.8	32.8	-0.5	0.6	7.2
		5535	15.4	34.3	0.2	0.5	7.3	1988	15.4	35.6	-0.5	0.3	7.6
	+6h	5536	15.9	18.2	0.2	0.7	4.0	1989	16.2	18.3	-0.4	0.6	4.1
		5537	15.8	20.6	0.2	0.5	4.5	1990	16.1	20.3	-0.4	0.8	4.5
22APR99	+24h	5538	15.2	29.8	0.2	0.7	6.3	1991	15.4	31.0	-0.5	0.8	6.6
		5539	15.3	29.1	0.2	0.6	6.2	1992	15.5	29.8	-0.5	0.7	6.4
23APR99	+48h	5540	15.6	43.4	0.1	0.7	9.4	1993	15.2	44.6	-0.5	1.0	9.4
		5541	16.2	38.8	0.1	0.7	8.7	1994	15.8	41.7	-0.5	0.9	9.2
24APR99	+72h	5543	15.7	15	0.5	0.6	3.3	1996	15.6	16.8	-0.1	0.6	3.6
		5544	15.6	15.7	0.5	0.7	3.4	1997	13.9	20.3	-0.2	0.7	3.9

ASTIN RH7AS Male Rhesus

19AUG98 WR242511 3.5 mg/kg

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK	SGOT	SGPT	Na	K	Cl
Pre	7.15	50.4	16.0	5.65	22.4	31.8	57	13.2	1.4	1175	81	75	152	5.0	104
+6h	6.59	45.7	14.7	12.6	22.2	32.0		17.0	0.8	11570	268	120			
+24h	6.63	46.7	15.6	9.32	23.6	33.4	62	10.5	1.2	4443	127	77	129	5.0	101
+48h	6.23	44.6	14.8	7.33	23.8	33.3	79	11.8	1.2	583	91	123	152	3.5	106
+120h	7.42	49.6	18.7	5.86	25.1	37.6	55	9.7	1.3	1354	114	129	155	4.0	111
+168h	5.78	41.2	13.4	4.81	23.2	32.5	65	13.4	1.2	194	54	102	150	3.8	111
+288h	5.62	39.9	14.0	6.76	24.9	35.1	64	15.3	1.4	117	60	87	152	4.2	111

14SEP98 PEG 200

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK	SGOT	SGPT	Na	K	Cl
BASE	6.16	43.3	14.4	6.32	23.3	33.2	57	12.4	1.2	60	43	55	149	3.2	104
+1hr	5.82	41.4	14.3	6.55	24.6	34.6	nd	11.9	nd	nd	66	53	nd	nd	Nd

ASTIN RH7AS Male Rhesus

19AUG98 3.5 mg/kg WR242511
Methemoglobin Sample Table

Time	Time from inj	Sam. #	OSM3 1(Print)					OSM3 2 (no print)				
			THb	HbO_2	HbCO	MHb	O2ct	THb	HbO_2	HbCO	MHb	O_2ct
19AUG98	PRE	1768	15.4	48.2	-0.4	0.4	10.3	15.3	28.7	0.0	0.4	6.1
		1769	14.8	29.1	-0.6	0.5	6.0					
	+1h	1772	14.3	41.9	-0.4	0.6	8.3	14.7	42.9	0.0	0.5	8.8
		1773	14.2	42.2	-0.5	0.7	8.3					
	+6h	1774	14.0	30.2	-0.2	0.6	5.9	15.0	28.2	0.1	0.8	5.9
		1775	14.6	29.9	-0.3	0.7	6.1					
20AUG98	+24h	1778	13.8	40.4	-0.5	0.8	7.7					
		1779	14.8	38.5	-0.6	1.1	7.5					
21AUG98	+48	1786	14.0	31.7	-0.3	1.1	6.2	14.3	30.4	0.1	1.1	6.0
		1787	14.0	31.6	-0.4	1.2	6.1					
22AUG98	+72h	1792	13.4	24.2	-0.4	1.5	4.5	13.6	23.2	0.1	1.3	4.4
		1793	13.3	24.4	-0.4	1.4	4.5					
23AUG98	+96h	1796	13.4	41.7	-0.6	1.7	7.8	13.8	40.4	-0.1	1.4	7.7
		1797	13.5	41.1	-0.5	1.5	7.7					
24AUG98	+120h	1801	13.2	19.2	-0.3	1.4	3.5	13.6	14.4	0.2	1.3	2.7
		1802	13.0	19.6	-0.3	1.3	3.5					
25AUG98	+144h	1805	12.7	51.0	-0.8	1.5	9.0	12.9	49.9	-0.3	1.2	8.9
		1806	12.7	50.4	-0.6	1.4	8.9	13.0	50.1	-0.3	1.1	9.1
26AUG98	+168h	1809	12.9	25.6	-0.5	1.3	4.6	13.1	24.0	0.1	0.9	4.4
		1810	12.8	24.4	-0.4	1.3	4.3	12.9	25..0	0.0	0.9	4.5
28AUG98	+216h	1813	12.3	69.7	-0.8	1.1	11.9	12.8	68.0	-0.3	0.9	12.1
		1814	12.9	68.9	-0.9	1.1	12.4	13.2	67.7	-0.4	1.1	12.4
29AUG98	+240h	1817	11.9	46.2	-0.7	1.1	7.6	12.0	45.0	0.0	0.7	7.5
								12.1	44.7	0.1	0.6	7.5
30AUG98	+264h	1819	13.2	46.8	-0.7	0.9	8.6	13.5	45.4	-0.2	0.8	8.5
31AUG98	+288h	1822	13.7	26.8	-0.5	0.9	5.1	14.0	25.7	0.1	0.5	5.0
		1823	13.8	27.3	-0.5	0.8	5.2	14.0	26.5	0.1	0.5	5.2

ASTIN RH7AS Male Rhesus

Methemoglobin Sample Table 14SEP98 PEG 200

Time	Time from inj	Sam. #	OSM3 1(Print)					OSM3 2 (no print)				
			THb	HbO_2	HbCO	MHb	O_2ct	THb	HbO_2	HbCO	MHb	O_2ct
14SEP98	BASE	1892	14.1	35.4	-0.5	0.6	6.9	14.5	34.1	0.0	0.4	6.9
		1893	14.0	38.2	-0.5	0.6	7.4					
	+1hr	1894	14.1	30.3	-0.3	0.5	5.9	14.6	30.3	0.0	0.5	6.1
		1895	14.1	30.2	-0.4	0.5	5.9					

Byron RH16999 Male Rhesus

03SEP98 WR242511 3.5 mg/kg IV

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK	SGOT	SGPT	Na	K	Cl
Base	6.06	39.2	13.1	7.9			81	13.3	1.6	96	35	52	151	3.5	108
+24h	6.30	41.2	13.4	14.6			XX	20.9	XX	435	101	37	XX	XX	XX
+120h	5.39	35.0	11.8	8.87			71	13.6	1.7	68	45	84	151	3.4	106
+144h	5.81	37.0	12.5	9.03			80	12.8	1.6	77	58	83	147	4.1	115
+168h	5.70	36.9	12.6	10.2			99	16.2	1.1	124	43	50	143	3.3	112
+192h	5.47	35.5	12.0	10.6			84	16.4	1.2	142	46	57	153	4.3	106

24SEP98 Exposure Multisol IV

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK	SGOT	SGPT	Na	K	Cl
Baseline	5.73	37.9	12.4	10.7	21.6	32.7	65	20.5	0.2	105	37	47			
+1hr	5.61	36.7	12.7	17.1	22.7	34.7	82	21.1	0.2	316	67	64	147	4.8	105
+6h	5.79 .	38.3	13.0	15.1	22.4	33.9	87	18.9	1.5	1219	78	60	148	4.1	105

3MAY99 Exposure Multisol Oral

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK	SGOT	SGPT	Na	K	Cl
Base	6.07	40.1	13.4	9.93	22.1	33.3	61	16.9	1.6	268		19	145	3.4	101
+1hr	6.41	42.3	14.5	17.5	22.6	34.2	40	15.3	1.7	656		23	145	3.5	104
+6hr	6.42	42.3	13.7	13.9	21.4	32.5	82	18.9	1.5	488		27	147	4.1	106
+24h	6.39	41.8	13.2	10.7	20.6	31.5	88	13.5	1.4	235		42	147	3.5	105
+72h	6.47	42.7	14.5	11.0	22.4	33.9	116	16.7	1.6	110		60	145	3.6	103
+96h	6.37	42.1	14.2	12.7	22.3	33.8	98	17.3	1.5	186		26	146	3.5	101

Byron RH16999 Male Rhesus

Methemoglobin Sample Table 03SEP98 WR242511 3.5 mg/kg IV

Time	Time from inj	Sam. #	OSM3 1(Print)					OSM3 2 (no print)				
			THb	HbO_2	HbCO	MHb	O2ct		THb	HbO_2	HbCO	MHb
03SEP98	Base	1840	13.1	55.0	-0.8	0.9	10.0	13.3	54.6	-0.5	0.7	10.1
		1841	12.8	61.1	-0.7	0.6	10.9					
	+1h	1846	12.4	37.4	-0.2	0.6	6.4	12.5	36.3	0.1	0.6	6.3
		1847	12.4	37.0	-0.3	0.6	6.4					
	+6h	1848	12.4	31.2	-0.2	0.8	5.4	12.8	30.1	0.2	0.7	5.4
		1849	12.5	30.7	-0.2	0.9	5.3	12.8	30.2	0.2	0.7	5.4
04SEP98	+24h	1850	13.1	36.5	-0.3	0.6	6.6	13.5	35.0	0.0	0.7	6.6
		1851	13.3	36.6	-0.4	0.7	6.8					
05SEP98	+48h	1856	12.2	53.6	-0.7	1.1	9.1	12.5	52.8	0.0	0.8	9.2
		1857	12.2	53.8	-0.6	1.0	9.1					
06SEP98	+72h	1862	11.6	30.6	-0.2	1.0	4.9	11.9	30.7	0.2	0.8	5.0
		1863	11.4	20.2	0.0	0.8	3.2					
07SEP98	+96h	1868	11.9	24.7	-0.1	0.9	4.1	11.9	27.9	0.1	1.0	4.6
		1869	11.4	28.9	-0.3	1.0	4.6					
08SEP98	+120h	1874	11.8	23.0	-0.4	1.1	3.8	12.4	20.2	0.0	1.0	3.5
		1875	11.9	22.4	-0.3	1.0	3.7					
09SEP98	+144h	1880	12.5	26.7	-0.4	0.8	4.6	12.8	25.6	0.0	1.0	4.6
		1881	12.5	26.0	-0.3	0.8	4.5					
10SEP98	+168h	1887	12.4	50.6	-0.6	0.8	8.7	12.5	50.4	-0.1	0.8	8.8
		1889	12.1	52.4	-0.7	0.9	8.8					
11SEP98	+198	1890	12.0	49.5	-0.6	1.0	8.3	12.0	48.9	0.0	0.7	8.2
		1891	9.8	54.8	-0.7	1.0	7.5					

Byron RH16999 Male Rhesus

24SEP98 Exposure Multisol IV
Methemoglobin Sample Table

Time	Time from inj	Sam. #	OSM3 1(Print)					OSM3 2 (no print)				
			THb	HbO_2	HbCO	MHb	O_2ct	THb	HbO_2	HbCO	MHb	O_2ct
24SEP98	Pre	1901	12.4	43.5	-0.6	0.5	7.5	12.8	41.9	-0.1	0.6	7.5
		1900	12.4	43.5	-0.5	0.6	7.5					
	+1hr	1902	12.0	40.9	-0.5	0.9	6.8	12.4	39.5	0.0	0.6	6.8
		1903	12.2	40.6	-0.4	0.7	6.98	12.3	40.1	0.1	0.4	6.9
		1904	12.1	40.2	-0.5	0.9	6.8					
	+6h	1905	12.5	35.5	-0.3	0.8	6.2	12.7	33.6	0.1	0.4	5.9
		1906	12.5	34.9	-0.4	0.7	6.1					

Methemoglobin Sample Table 3MAY99 Exposure Multisol Oral

Time	Time from inj	Sam. #	OSM3 A					OSM3 B					
			THb	HbO_2	HbCO	MHb	O_2ct	Sample	THb	HbO_2	HbCO	MHb	O_2ct
3MAY99	Base	5546	13.1	64.1	-0.2	0.5	11.7	1999	12.9	65.8	-0.9	0.7	11.8
		5547	13.5	63.8	-0.2	0.5	12.0	2000	13.5	63.5	-0.9	0.6	11.9
	+1hr	5548	13.8	39.2	0.0	0.5	7.5	2001	13.8	40.9	-0.6	0.6	7.8
		5549	14.0	38.8	0.1	0.4	7.6	2002	14.0	38.8	-0.6	0.4	7.6
	+6hr	5550	13.8	41.4	-0.1	0.7	7.9	2003	13.9	41.8	-0.6	0.7	8.1
		5551	13.7	37.5	0.0	0.6	7.1	2004	13.8	37.2	-0.5	0.5	7.1
4MAY99	+24hr	5552	13.7	56.8	-0.1	0.7	10.8	2005	13.7	58.6	-0.7	0.6	11.2
		5553	13.6	64.1	-0.2	0.6	12.1	2006	13.8	62.9	-0.7	0.6	12.1
5MAY99	+48hr	5554	13.8	46.8	-0.2	0.6	9.0	2007	13.9	50.6	-0.7	0.6	9.8
		5555	13.9	49.7	-0.1	0.5	9.6	2008	13.8	54.4	-0.7	0.5	10.4
6MAY99	+72hr	5556	13.7	67.2	-0.2	0.4	12.8	2009	12.6	92.6	-1.1	0.1	16.2
								2010	13.8	66.7	-0.9	0.6	12.8
7MAY99	+96hr	5557	123.3	48.4	-0.2	0.5	8.9	2011	13.6	45.2	-0.6	0.5	8.5
		5558	13.3	47.9	-0.2	0.6	8.9	2012	13.5	45.3	-0.7	0.6	8.5

Kong RHF942Male Rhesus

1SEP98 Exposure 3.5 mg/kg WR 242511 IV

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK	SGOT	SGPT	Na	K	Cl
Base	7.04	51.1	17.1	9.04	24.3	33.6	56	14.3	1.5	53	51	62	153	4.0	107
+24h	6.41	46.6	15.3	7.86	23.9	32.9	81	11.2	1.6	213	74	75	151	4.3	101
+48h	5.75	41.4	14.7	10.5	25.5	35.5	62	10.1	1.5	342	54	75	154	3.7	108
+72h	6.03	43.0	14.9	9.27	24.7	34.7	73	11.5	1.3	37	46	30	151	3.5	104
+168h	5.98	43.4	14.8	7.57	24.8	34.2	79	12.3	1.7	63	43	53	154	3.9	107
+192h	6.36	46.5	15.4	9.08	24.2	33.1	92	11.2	1.7	75	45	59	160	5.9	103

7JAN98 Exposure Telazol Only MHb

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK	SGOT	SGPT	Na	K	Cl
08:40	5.78	42.0	14.6	7.24	25.2	34.7	47	15.6	1.5	ND	ND	43	150	3.8	112

13JAN99 Exposure WR242511 7.0 mg/kg IV SLOW (60 minutes)

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK	SGOT	SGPT	Na	K	Cl
Pre	4.87	35.1	11.3	4.53	23.2	32.2	32	15.3	1.8	290		25	150	6.0	116
5min	4.98	36.3	12.4	4.17	24.8	34.1	44	15.7	2.1	340		24	149	7.3	115
1h	4.97	36.1	12.3	4.01	24.8	34.1	55	17.0	1.9	475		23	150	4.6	117
6h	6.15	44.3	15.2	12.7	24.6	34.3	182	19.2	1.9	5535		39	148	5.3	110
24h	5.69	41.0	14.1	7.63	24.8	34.4	78	9.8	1.6	960		50	152	3.3	106
48h	5.42	40.2	13.6	9.62	25.1	33.9	116	8.7	1.7	225		42	151	3.7	103
144h	5.61	41.0	13.8	8.44	24.7	33.8	109	10.7	1.8	638		57	145	3.3	107
168h	5.81	42.4	13.8	7.7	23.7	32.4	102	11.9	1.6	223		60	152	3.6	109
192h	5.71	41.8	13.0	8.07	22.9	31.2	92	10.3	1.6	86		39	147	3.5	103
216h	5.79	43.1	13.7	12.0	23.7	31.9	100	7.8	1.6	65		46	152	3.8	100

Kong RHF942Male Rhesus

Methemoglobin Sample Table 1SEP98 Exposure 3.5 mg/kg WR 242511 IV

Date	Time from inj	Sam. #	OSM3 1(Print)					OSM3 2 (no print)				
			THb	HbO_2	HbCO	MHb	O2ct		THb	HbO_2	HbCO	MHb
01SEP98	Base	1824	15.0	40.0	-0.5	0.6	8.3	15.1	39.6	0.2	0.3	8.3
		1825	15.1	39.7	-0.5	0.5	8.3					
	+1h	1828	14.7	26.6	-0.2	0.4	5.4	15.0	29.1	0.3	0.5	6.1
		1829	14.7	34.1	-0.4	0.6	7.0					
	+6h	1832	14.3	30.8	-0.2	0.8	6.1	14.9	33.1	0.3	0.5	6.9
02SEP98	+24h	1836	15.3	38.1	-0.5	0.9	8.1	15.5	38.1	-0.2	0.9	8.2
		1837	15.1	44.5	-0.6	0.9	9.3					
03SEP98	+48h	1842	13.8	41.7	-0.4	0.8	8.0	14.2	41.0	-0.2	0.7	8.1
		1843	14.0	40.7	-0.3	0.7	7.9					
04SEP98	+72h	1852	14.1	46.6	-0.5	1.0	9.1	14.2	45.2	-0.1	0.8	8.9
		1853	13.8	44.7	-0.5	1.0	8.6					
05SEP98	+96h	1858	14.1	55.1	-0.7	0.9	10.8	14.1	52.8	-0.1	0.7	10.3
		1859	12.2	57.4	-0.8	1.1	9.7					
06SEP98	+120h	1864	14.0	37.7	-0.2	0.7	7.3	14.2	40.4	0.1	0.6	8.0
		1865	13.5	41.5	-0.3	0.6	7.8					
07SEP98	+144h	1870	14.5	9.8	-0.2	0.7	2.0	14.4	10.4	0.2	0.6	2.1
		1871	13.9	11.2	-0.1	0.7	2.2					
08SEP98	+168h	1876	13.8	42.5	-0.6	0.7	8.2	14.2	40.6	-0.2	0.7	8.0
		1877	13.7	44.3	-0.5	0.7	8.4					
09SEP98	+192h	1882	14.9	16.7	-0.2	0.3	3.5	15.1	16.0	0.2	0.5	3.4
		1883	14.8	17.9	-0.4	0.6	3.7					
		1884	14.7	19.7	-0.3	0.6	4.0					

Methemoglobin Sample Table 7JAN99 Telazol only

Time	Time from inj	Sam. #	OSM3 1(Print)					OSM3 2 (no print)				
			THb	HbO_2	HbCO	MHb	O_2ct	THb	HbO_2	HbCO	MHb	O_2ct
08:40	Tel +10m	1943	13.7	70.3	-0.6	0.5	13.4	14.0	70.1	0.1	0.2	13.6
		1944	13.8	71.8	-0.5	0.5	13.8	14.1	71.2	0.0	0.3	14.0
08:45	Tel+15m	1945	13.4	56.2	-0.4	0.4	10.5	13.5	56.3	0.1	0.4	10.6
		1946	13.3	57.9	-0.4	0.4	10.7	13.7	57.1	0.1	0.4	10.9

Kong RHF942Male Rhesus

★ Methemoglobin Sample Table 13JAN98 Exposure WR242511 7.0 mg/kg IV SLOW (60 minutes)

Time	Time from inj	Sam. #	OSM3 1(Print)					OSM3 2 (no print)				
			THb	HbO_2	HbCO	MHb	O_2ct	THb	HbO_2	HbCO	MHb	O_2ct
13JAN99	0	1947	12.7	97.1	-0.7	0.3	17.1	13.0	96.5	-0.1	0.4	17.4
		1948	13.0	96.6	-0.8	0.5	17.5					
	+5min	1949	12.6	95.2	-0.6	0.5	16.7	12.6	95.1	0.2	0.4	15.7
		1950	12.5	95.2	-0.7	0.5	16.5					
	+1hr	1951	12.7	94.6	-0.6	0.7	16.7	13.0	93.7	0.3	0.5	16.9
		1952	12.7	95.2	-0.5	0.5	16.8					
	+6hr	1953	14.5	51.6	-0.1	0.5	10.4	15.0	50.2	0.4	0.6	10.5
		1954	14.7	52.4	-0.2	0.6	10.7					
14JAN99	+24h	1955	13.3	50.3	-0.6	0.6	9.3	13.9	49.5	-0.1	0.5	9.6
		1956	13.5	50	-0.6	0.6	9.4					
15JAN99	+48h	1957	13.4	28.3	-0.4	0.7	5.3	13.7	27.0	0.3	0.4	5.1
		1958	13.5	27.7	-0.4	0.6	5.2					
16JAN99	+72h	1959	13.8	43.4	-0.4	0.5	8.3	14.1	42.0	0.1	0.5	8.2
		1960	13.9	43.3	-0.6	0.7	8.4					
17JAN99	+96h	1961	14.0	17.7	-0.3	0.5	3.4	14.1	16.5	0.1	0.6	3.2
		1962	13.8	18.1	-0.4	0.7	3.5					
18JAN99	+120h	1963	13.8	29.0	-0.7	0.7	5.6	14.3	28.9	0.1	0.4	5.7
		1964	13.9	32.7	-0.7	0.8	6.3	14.4	35.0	-0.1	0.6	7.0
19JAN99	+144h	1965	13.5	24.7	-0.4	0.6	4.8	13.8	23.6	0.1	0.7	4.5
		1966	13.5	38.2	-0.5	0.6	7.2					
20JAN99	+168h	1967	13.9	37.6	-0.4	0.4	7.3	14.2	34.8	0.1	0.6	6.9
		1968	13.5	60.2	-0.7	0.6	11.3					
21JAN99	+192h	1969	13.6	35.1	-0.5	0.6	6.6	13.8	34.5	0.1	0.4	6.6
		1970	13.5	37.3	-0.5	0.6	7.0					
22JAN99	+216h	1971	14.3	13.4	-0.3	0.5	2.7	14.5	13.4	0.3	0.4	2.7
		1972	14.1	17.3	-0.3	0.6	3.4	14.4	16.5	0.2	0.5	3.3

JOE RHJW0 Male Rhesus

1SEP98 Exposure WR242511 3.5 mg/kg IV

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK	SGOT	SGPT	Na	K	Cl
Base	7.21	51.7	17.7	17.5	24.5	34.2	98	10.5	1.7	77	47	51	153	3.4	103
+24h	5.74	41.0	13.4	19.3	23.4	32.7	85	8.4	1.6	4024	100	84	153	3.8	103
+48h	5.41	38.7	14.0	14.6	25.9	36.2	73	13.3	1.6	201	58	84	154	3.6	100
+72h	5.37	38.4	13.0	15.7	24.2	33.8	76	11.5	1.5	966	75	50	151	3.9	106
+168h	5.36	37.7	13.1	13.7	24.5	34.8	68	11.8	1.5	61	52	52	92	2.5	65
+192h	5.55	39.1	13.6	15.0	24.5	34.7	82	10.8	1.8	1200	39	58	151	3.5	104

29SEP – 1OCT98 Exposure WR 242511 7.0 mg/kg IV (Died)

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK	SGOT	SGPT	Na	K	Cl
Base	4.98	31.3	14.9	22.1	30	47.7	77	10.2	1.6	40	31	30	150	3.6	114
1h	6.15	43.7	14.8	19.7	24.2	34.0	94	10.7	1.7	75	134	37	149	3.9	124
24h	6.07	43.5	14.3	21.2	23.5	32.8		10.3	1.2	1690	82	45			

"Joe" RH – JW0 WT 9.8 kgs

Methemoglobin Sample Table

Date	Time from inj	Sam. #	OSM3 1(Print)					OSM3 2 (no print)				
			THb	HbO_2	HbCO	MHb	O2ct		THb	HbO_2	HbCO	MHb
01SEP98	Base	1826	14.4	39.0	-0.5	0.6	7.8	14.7	39.1	0.1	0.4	8.0
		1827	14.5	40.1	-0.5	0.7	8.1					
	+1h	1830	13.0	55.1	-0.4	0.7	10.0	13.3	54.3	0.1	0.5	10.0
		1831	13.1	56.7	-0.4	0.6	10.3					
	+6h	1834	13.4	46.4	-0.1	0.6	8.6	13.6	47.7	0.3	0.6	9.0
		1835	13.4	49.9	-0.2	0.7	9.3					
02SEP98	+24h	1838	13.2	46.1	-0.6	1.1	8.5	13.4	45.7	-0.2	0.8	8.5
		1839	13.1	47.1	-0.6	1.0	8.6					
03SEP98	+48h	1844	13.3	32.7	-0.3	0.9	6.0	13.7	31.5	-0.1	0.8	6.0
		1845	13.3	31.5	-0.3	0.9	5.8					
04SEP98	+72h	1854	12.6	35.7	-0.4	1.1	6.3	12.8	36.0	0.0	0.8	6.4
		1855	12.6	38.2	-0.6	1.1	6.7					
05SEP98	+96h	1860	13.7	24.2	-0.5	1.0	4.6	13.8	23.2	0.2	0.6	4.5
		1861	13.5	24.0	-0.4	0.8	4.5					
06SEP98	+120h	1866	12.6	20.9	-0.1	0.6	3.7	12.6	20.3	0.4	0.4	3.6
		1867	11.7	25.8	-0.1	0.7	4.2					
07SEP98	+144h	1873	12.9	29.3	-0.4	0.8	5.3	13.5	30.8	0.1	0.7	5.8
08SEP98	+168h	1878	12.8	38.8	-0.2	0.6	6.9	13.1	38.9	0.1	0.6	7.1
		1879	12.8	41.4	-0.3	0.6	7.4					
09SEP98	+192h	1885	13.2	46.2	-0.5	0.6	8.5	13.4	45.7	0.0	0.5	8.5
		1886	12.8	52.0	-0.5	0.6	9.3					

JOE RHJW0 Male Rhesus

29SEP – 1OCT98 Exposure WR 242511 7.0 mg/kg IV (Died)

Methemoglobin Sample Table

Date	Time from inj	Sam. #	OSM3 1(Print)					OSM3 2 (no print)				
			THb	HbO_2	HbCO	MHb	O2ct	THb	HbO_2	HbCO	MHb	O2ct
29SEP98	Base	1910	14.5	55.0	-0.5	0.5	11.1	14.8	54.5	0.1	0.5	11.2
		1911	14.5	55.4	-0.6	0.6	11.2					
	+1h	1914	14.5	61.2	-0.5	0.7	12.3	14.8	59.7	0.2	0.7	12.3
		1915	14.4	60.6	-0.5	0.6	12.1					
	+6h	1918	14.0	15.0	0.2	1.0	2.9	14.5	14.8	0.8	0.6	3.0
		1919	14.3	15.3	0.2	1.0	3.0					
30SEP98	+24h	1922	14.0	53.1	-0.4	0.8	10.3	14.1	52.7	0.2	0.5	10.3

Nancy RH 90B055 Female Rhesus

20AUG98 WR242511 3.5 mg/kg IV

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK	SGOT	SGPT	Na	K	Cl
Pre	5.14	37.0	12.9	6.47	25.0	34.7	74	23.1	1.4	55	52	33	131	6.3	107
+24h	4.56	33.4	11.5	5.72	25.2	34.4	88	21.7	1.3	319	85	43	149	3.7	105
+96h	6.17	45.0	15.0	11.00	24.3	33.3	36	20.9	1.4	109	80	50	149	3.9	106
+144h	4.47	33.3	11.7	6.25	26.3	35.2	80	19.1	1.2	208	49	43	149	3.6	110
+264h	4.55	33.3	12.1	5.67	26.6	36.3	81	17.3	1.2	34	45	42	148	3.6	102

Nancy RH 90B055 Female Rhesus

Methemoglobin Sample Table 20AUG98 WR242511 3.5 mg/kg IV

Time	Time from inj	Sam #	OSM3 1(Print)					OSM3 2 (no print)				
			THb	HbO_2	HbCO	MHb	O2ct	THb	HbO_2	HbCO	MHb	02ct
20AUG98	Pre	1776	12.4	62.0	-0.8	0.6	10.7	12.7	61.2	-0.3	0.6	10.8
		1777	12.6	62.2	-0.8	0.6	10.9					
	+1h	1780	12.1	62.5	-0.7	0.7	10.5	12.5	60.9	0.0	0.4	10.6
		1781	12.0	64.1	-0.7	0.7	10.7					
	+6h	1783	12.1	40.6	-0.2	1.0	6.8	12.6	38.3	0.2	0.9	6.7
		1784	12.5	38.7	-0.3	1.0	6.7	12.7	36.4	0.2	0.9	6.4
21AUG98	+24h	1785	11.3	49.3	-0.5	2.9	7.7	11.4	45.1	-0.2	2.9	7.1
		2ndB						11.6	46.8	-0.1	2.8	7.5
22AUG98	+48h	1790	11.8	58.2	-0.6	3.9	9.5	12.1	54.8	-0.1	3.6	9.2
		1791	11.6	54.9	-0.7	4.0	8.9					
23AUG98	+72h	1794	12.3	47.0	-0.6	3.3	8.0	12.6	44.5	0.0	2.9	7.8
		1795	12.6	44.6	-0.6	3.3	7.8					
24AUG98	+96h	1798	12.0	51.2	-0.7	2.7	8.5	12.1	50.4	0.0	2.3	8.5
		1799	12.1	51.1	-0.6	2.5	8.6					
25AUG98	+120h	1803	11.3	31.7	-0.4	2.0	5.0	11.5	31.3	0.0	1.7	5.0
		1804	11.3	33.8	-0.5	2.0	5.3	11.6	33.6	0.0	1.6	5.4
26AUG98	+144h	1807	11.2	44.1	-0.6	1.6	6.9	11.5	43.3	0.0	1.4	6.9
		18.8	11.1	44.3	-0.5	1.5	6.8					
28AUG98	+192h	1811	11.8	53.3	-0.6	1.2	8.7	11.9	52.9	-0.2	1.0	8.8
		1812	11.8	54.1	-0.7	1.3	8.9	12.1	52.3	-0.1	0.9	8.8
29AUG98	+216h	1815	11.8	38.3	-0.5	1.0	6.3	12.1	33.8	0.2	0.8	5.7
30AUG98	+240h	1818	11.3	31.3	-0.4	0.9	4.9	11.5	28.8	0.2	0.7	4.6
31AUG98	+264h	1820	11.6	60.2	-0.7	0.9	9.7	11.5	60.3	-0.2	0.7	9.6
		1821	11.4	60.5	-0.6	0.9	9.6	11.7	59.7	-0.1	0.6	9.7

Nancy RH 90B055 Female Rhesus

20AUG98 WR242511 3.5 mg/kg IV

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK	SGOT	SGPT	Na	K	Cl
Pre	5.14	37.0	12.9	6.47	25.0	34.7	74	23.1	1.4	55	52	33	131	6.3	107
+24h	4.56	33.4	11.5	5.72	25.2	34.4	88	21.7	1.3	319	85	43	149	3.7	105
+96h	6.17	45.0	15.0	11.00	24.3	33.3	36	20.9	1.4	109	80	50	149	3.9	106
+144h	4.47	33.3	11.7	6.25	26.3	35.2	80	19.1	1.2	208	49	43	149	3.6	110
+264h	4.55	33.3	12.1	5.67	26.6	36.3	81	17.3	1.2	34	45	42	148	3.6	102

Nancy RH 90B055 Female Rhesus

Methemoglobin Sample Table 20AUG98 WR242511 3.5 mg/kg IV

Time	Time from inj	Sam. #	OSM3 1(Print)					OSM3 2 (no print)				
			THb	HbO_2	HbCO	MHb	O2ct	THb	HbO_2	HbCO	MHb	02ct
20AUG98	Pre	1776	12.4	62.0	-0.8	0.6	10.7	12.7	61.2	-0.3	0.6	10.8
		1777	12.6	62.2	-0.8	0.6	10.9					
	+1h	1780	12.1	62.5	-0.7	0.7	10.5	12.5	60.9	0.0	0.4	10.6
		1781	12.0	64.1	-0.7	0.7	10.7					
	+6h	1783	12.1	40.6	-0.2	1.0	6.8	12.6	38.3	0.2	0.9	6.7
		1784	12.5	38.7	-0.3	1.0	6.7	12.7	36.4	0.2	0.9	6.4
21AUG98	+24h	1785	11.3	49.3	-0.5	2.9	7.7	11.4	45.1	-0.2	2.9	7.1
		2ndB						11.6	46.8	-0.1	2.8	7.5
22AUG98	+48h	1790	11.8	58.2	-0.6	3.9	9.5	12.1	54.8	-0.1	3.6	9.2
		1791	11.6	54.9	-0.7	4.0	8.9					
23AUG98	+72h	1794	12.3	47.0	-0.6	3.3	8.0	12.6	44.5	0.0	2.9	7.8
		1795	12.6	44.6	-0.6	3.3	7.8					
24AUG98	+96h	1798	12.0	51.2	-0.7	2.7	8.5	12.1	50.4	0.0	2.3	8.5
		1799	12.1	51.1	-0.6	2.5	8.6					
25AUG98	+120h	1803	11.3	31.7	-0.4	2.0	5.0	11.5	31.3	0.0	1.7	5.0
		1804	11.3	33.8	-0.5	2.0	5.3	11.6	33.6	0.0	1.6	5.4
26AUG98	+144h	1807	11.2	44.1	-0.6	1.6	6.9	11.5	43.3	0.0	1.4	6.9
		18.8	11.1	44.3	-0.5	1.5	6.8					
28AUG98	+192h	1811	11.8	53.3	-0.6	1.2	8.7	11.9	52.9	-0.2	1.0	8.8
		1812	11.8	54.1	-0.7	1.3	8.9	12.1	52.3	-0.1	0.9	8.8
29AUG98	+216h	1815	11.8	38.3	-0.5	1.0	6.3	12.1	33.8	0.2	0.8	5.7
30AUG98	+240h	1818	11.3	31.3	-0.4	0.9	4.9	11.5	28.8	0.2	0.7	4.6
31AUG98	+264h	1820	11.6	60.2	-0.7	0.9	9.7	11.5	60.3	-0.2	0.7	9.6
		1821	11.4	60.5	-0.6	0.9	9.6	11.7	59.7	-0.1	0.6	9.7

N:/pccommon/AVMoran/Mhbr/drugblood

Sheba, RH P3C Female Rhesus

P3C Sheba - 13AUG98 WR242511 3.5 mg/kg IV

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK	SGOT	SGPT	Na	K	Cl
PRE	6.44	43.6	14.4	3.63	22.4	33.2	79	16.5	0.8	3	38	22	147	4.3	98
+96h	5.99	41.0	14.0	3.74	23.4	34.1									
+120h							68	11.6	1.7	4	39	50	150	4.9	94
+8d	5.37	36.1	11.8	3.42	22.0	32.8	60	20.4	1.4	138	47	48	149	3.8	107

P3C Sheba – 29SEP98 WR242511 7.0 mg/kg IV

Hematology and serum chemistry															
Time	RBC	HCT	HGB	WBC	MCH	MCHC	GLU	BUN	CRE	CPK	SGOT	SGPT	Na	K	Cl
Base	5.95	40.7	14.1	6.86	23.7	34.6	62	24.1	1.4	48	61	110	151	4.1	113
+1hr	6.33	43.0	14.2	5.61	22.4	32.9	71	24.4	1.5	280	189	108	148	4.9	120
+24h	6.09	41.5	14.2	19.4	23.3	34.2	85	27.1	1.7	334	77	93	148	4.0	107
+48h	5.90	39.4	13.3	13.3	22.6	33.8	79	23.2	1.2	100	83	82	147	5.3	104
+72h	4.41	30.0	9.97	7.94	22.6	33.3	68	21.2	1.4	1	62	43			
+216h	5.57	37.8	13.2	20.0	23.7	35.0	76	21.0	1.3	75	2	19	147	3.8	102

Sheba, RH P3C Female Rhesus

Methemoglobin Sample Table

21AUG98 3.5 mg/kg WR242511

Time	Time from inj	Sam #	OSM3 1(Print)					OSM3 2 (no print)				
			THb	HbO_2	$HbCO_2$	Mhb	O_2ct	THb	HbO_2	$HbCO_2$	MHb	O_2ct
13AUG	Pre	1750	13.3	57.1	-0.6	0.6	10.6					
		1751	13.1	57.7	-0.7	0.6	10.5					
	+1hr	1752	12.0	47.8	-0.3	0.7	8.0					
		1753	11.9	47.6	-0.4	0.6	7.9					
		1754	12.2	48.0	-0.3	0.7	8.1					
	+6hr	1755	12.8	28.6	-0.2	0.6	5.1					
		1756	12.6	44.0	-0.3	0.6	7.7					
14AUG	+24hr	1757	12.8	67.9	-0.6	0.6	12.1					
		1758	12.6	65.7	-0.5	0.5	11.5					
15AUG	+48hr	1759	13.1	73.5	-0.6	0.6	13.4					
		1760	13.0	73.7	-0.7	0.7	13.3					
16AUG	+72hr	1761	12.2	75.5	-0.8	0.9	12.8					
		1762	12.4	77.5	-0.9	0.9	13.4					
17AUG	+96hr	1763	12.6	32.9	-0.5	0.7	5.8					
		1764	12.6	32.9	-0.4	0.6	5.8					
		1765	12.6	39.6	-0.6	0.8	6.9					
18AUG	+120hr	1766	12.1	24.7	-0.4	0.7	4.3	12.3	23.6	-0.1	0.5	4.0
		1767	12.4	23.7	-0.4	0.8	4.1	12.6	20.3	-0.1	0.7	3.6
19AUG	+144hr	1770	10.6	47.2	-0.4	0.8	7.0	10.8	52.0	-0.1	0.6	7.8
		1771	10.2	54.9	-0.5	0.8	7.8					
20AUG	+168hr	1782	12.1	46.1	-0.6	0.7	7.8	12.1	47.5	-0.2	0.8	8.0
21AUG	+192hr	1788	11.6	44.1	-0.5	0.6	7.1	11.9	42.7	-0.1	0.6	7.1
		1789	11.6	46.6	-0.6	0.7	7.5					

Sheba, RH P3C Female Rhesus

Methemoglobin Sample Table
29SEP98 7.0 mg/kg WR242511

Time	Time from inj	Sam. #	OSM3 1(Print)					OSM3 2 (no print)				
			THb	HbO_2	HbCO	MHb	O_2ct	THb	HbO_2	HbCO	MHb	O_2ct
29SEP98	Base	1908	14.0	38.1	-0.6	0.4	7.4	14.1	37.2	-0.1	0.6	7.3
		1909	13.9	38.9	-0.6	0.5	7.5					
	+1h	1912	14.5	49.6	-0.5	0.7	10.0	14.7	49.2	0.0	0.8	10.1
		1913	14.3	55.3	-0.6	0.7	11.0					
	+6h	1916	14.3	15.6	0.0	0.8	3.1	15.2	14.6	0.5	0.7	3.1
		1917	14.9	16.1	0.0	0.3	3.1					
30SEP98	+24h	1920	13.8	41.6	-0.5	0.7	8.0	14.1	41.0	0.0	0.6	8.0
		1921	13.7	41.7	-0.6	0.8	7.9					
01OCT98	+48h	1923	12.6	30.0	-0.5	0.9	5.3	12.8	29.9	-0.1	0.8	5.3
		1924	12.6	30.2	-0.5	0.8	5.3					
02OCT98	+72h	1925	10.1	39.2	-0.4	1.1	5.5	10.5	37.6	0.0	1.1	5.5
		1926	10.4	39.5	-0.5	1.1	5.7					
03OCT98	+96h	1927	10.6	32.8	-0.5	1.3	4.8					
04OCT98	+120h	1928	10.7	32.0	-0.5	1.1	4.8	11.2	31.3	-0.1	0.9	4.9
08OCT98	+216	1929	12.5	19.0	-0.4	0.8	3.3	12.8	17.1	0.1	0.5	3.0
		1930	12.3	17.3	-0.3	0.6	3.0					

Appendix G. Original Necropsy Reports

VETERINARY PATHOLOGY REPORT

U.S. Army Medical Research Institute
of Chemical Defense
Aberdeen Proving Grounds, MD 21010-5425

updated

ACCESSION NUMBER:
98-1392

VENDOR:	DATE RECEIVED:	INVESTIGATOR:	PROTOCOL NUMBER:
		Rockwood/Baskin	ICD-Diagnostic

SPECIES:	BREED/STRAIN:	SEX:	AGE:	ANIMAL I.D.:
NHP	Rhesus	M		JWO

DATE OF DEATH:	DATE OF NECROPSY:	PROSECTOR:
	10/01/98	Micheltree

HISTORY:

This 10.0 kg male Rhesus monkey had received an IV injection of WR 242511 on two separate occasions. The initial solution was prepared in PEG200. Later, because darkened urine was observed in the animal within 1 hr. post-injection, a different solvent (multisol) was used for the 2nd injection. Again, darkened urine was noted within 1 hr post injection and determined to be hemoglobin. It was noted on 30 Sept 98 that JWO had vomited overnight, and had loose stools. It was also noted that day that he was pale, lethargic, and not eating. The animal was given gatorade and a cover, as the animal was shivering. JWO was found dead in its cage at 0730 on 1 OCT 1998.

GROSS FINDINGS:

The carcass was in good flesh and there were no significant gross lesions.

Clinical pathology revealed no significant findings. Bone marrow examination is pending.

MICROSCOPIC DIAGNOSIS(ES):

1. Lungs: Edema, alveolar, acute, diffuse, severe, with marked fibrinous exudate, fibrin thrombi, and alveolar macrophages that contain an acidophilic globular material.
2. Heart, myocardial interstitium: Myocarditis, subacute, multifocal, mild, with focal fibrosis and mild epicardial hemorrhage.
3. Liver: Congestion, acute, diffuse, marked.
4. Liver, hepatocytes: Vacuolar degeneration, diffuse, severe.
5. Stomach: Gastritis, lymphohistiocytic, multifocal moderate.
6. Kidney: Congestion, acute, diffuse, moderate, with mild tubular degeneration and rare leukocyte casts.
7. Adrenal glands: Congestion, acute, diffuse, moderate.

COMMENTS:

The combination of clinical signs, pulmonary edema, heart lesions, and multiorgan congestion indicates that this animal died of severe cardiopulmonary dysfunction

VETERINARY PATHOLOGY REPORT

U.S. Army Medical Research Institute
of Chemical Defense
Aberdeen Proving Grounds, MD 21010-5425

ACCESSION NUMBER:
98-1392

(continued)

(hypotensive shock leading to acute congestive heart failure). The pulmonary thrombosis and hemoglobinuria suggests a hematologic disorder as the inciting cause. Differential diagnoses in this case would include direct toxic or oxidative destruction of red blood cells (intravascular hemolysis), and possibly a coagulation syndrome. The acute nature of the condition negated accurate hematologic assessment. Vacuolar degeneration of hepatocytes is commonly seen in other species due to an increase in exogenous or endogenous corticosteroids; however, some form of toxic effect on the liver cannot be ruled out. The lesions in the kidney were minimal, but may also suggest a toxicity. The cause of the gastritis was not evident histologically.

REPORTED BY:

Crystal M. Briscoe

Crystal M. Briscoe, MAJ, VC
Veterinary Pathologist
Diplomate, ACVP
Comparative Pathology Branch

DATE: 10/22/98

VETERINARY PATHOLOGY REPORT

U.S. Army Medical Research Institute
of Chemical Defense
Aberdeen Proving Grounds, MD 21010-5425

DATE: 04/27/99

ACCESSION NUMBER:
99-391

Vendor:	Date received:	Investigators: Dr Rockwood	Protocol number:

Species:	Breed/Strain:	Sex:	Age:	Animal ID:
NHP	Rhesus	M	Adult	6VY

Date of Death:	Date of Necropsy:	Prosector:
25 April 1999	26 April 1999	MAJ Duniho

HISTORY: Deteriorating health since 23 April 1999 with episodes of vomiting and labored breathing. Treated with intravenous fluids. Blood and coagulated blood noted in oral cavity at death.

GROSS FINDINGS:

1. General: Tattoo on inner left thigh labeled as "6VY". Superficial abrasion with 2 cm scab surrounded by hyperemia on left inguinal/abdominal area.
Presented in good body condition with ample subcutaneous and cavitary fat. Stomach is filled with partially digested granular material. Intestines contain soft, brown digested material, and colon contains formed fecal pellets.
Left upper canine fractured. Bilateral buccal laceration on upper and lower lips at the level of canine teeth.
2. Subcutis: Multifocal subcutaneous ecchymoses and hemorrhages ranging from 0.5 to 4 cm on the back extending from the scapular to the lumbar area.
3. Thoracic cavity and heart: Multifocal hemorrhages on epicardium and thoracic wall ranging from 2mm to 2cm in diameter. Superficial subendocardial hemorrhage on interventricular septum in left ventricle 3 cm in diameter.
4. Lungs: Diffuse congestion.
5. Larynx and trachea: Small amounts of regurgitated, partially digested food particles in larynx, and small amounts of brown food particles admixed with mucus.
6. Liver: Diffuse centrilobular white discoloration with superficial, serosal up to 1 cm white nodules.
7. Colon: Multifocal colonic mesenteric nodules/saccules measuring up to 0.5 cm.

MICROSCOPIC DIAGNOSIS(ES): Histopathologic report to follow.

COMMENTS: The blood in the oral cavity noted at death is most likely the result of self-inflicted lip lacerations caused by teeth trauma. The cause of the subcutaneous, thoracic and cardiac hemorrhages cannot be determined frrom the gross necropsy examination. The presence of food particles in the larynx and trachea indicate regurgitation followed by aspiration into the respiratory tract. The exact nature of the liver changes will be determined histologically The cause of death is not apparent from the gross necropsy examination.

Steven Duniho

STEVEN M DUNIHO
MAJ, VC
VETERINARY PATHOLOGIST

VETERINARY PATHOLOGY REPORT

11May99

U.S. Army Medical Research Institute
of Chemical Defense
Aberdeen Proving Grounds, MD 21010-5425

ACCESSION NUMBER :
99-0391

VENDOR:	DATE RECEIVED:	INVESTIGATOR:	PROTOCOL NUMBER:
		Dr Rockwood	Diagnostic

SPECIES:	BREED/STRAIN:	SEX:	AGE:	ANIMAL I.D.:
NHP	Rhesus monkey	M		6VY

DATE OF DEATH:	DATE OF NECROPSY:	PROSECTOR:
04/25/99	04/26/99	MAJ Duniho

HISTORY:

See previous pathology report dated 04/27/99

GROSS FINDINGS:

See previous pathology report dated 04/27/99

MICROSCOPIC DIAGNOSIS(ES):

1. Liver, hepatocytes: Degeneration and necrosis, submassive, acute, diffuse, with severe congestion.
2. Kidney: Tubular degeneration and necrosis, diffuse, moderate to severe, with multifocal cellular, granular and hemoglobin casts, and tubular and glomerular protein.
3. Adrenal gland, zona reticularis: Necrosis, acute, diffuse.
4. Heart: Hemorrhage, acute, subendocardial and myocardial, multifocal, mild, with myocardial degeneration.
5. Spleen: Congestion, difuse, moderate.
6. Esophagus, periesophageal fibroadipose tissue: Hemorrhage, acute, focally extensive, moderate.
7. Pancreas: Hemorrhage, acute, periductular, focally extensive, mild.
8. Meninges: Hemorrhage, acute, multifocal, mild.
9. Pericardium: Hemorrhage, acute, multifocal, mild with fibrin thrombi.
10. Thymus: Hemorrhage, acute, multifocal, moderate.
11. Esophagus, skeletal muscle: Myositis, chronic, multifocal, moderate, with myofiber loss and regeneration.
12. Skin, inguinal area: Dermatitis, subacute, perivascular, multifocal, mild, with hemorrhage and fibrin microthrombi.
13. Fibroadipose tissue, mesentery: Fat necrosis, nodular, focal.
14. Heart: Myocarditis, lymphoplasmacytic, multifocal, minimal.
15. Lung; trachea; thyroid gland; tonsil; salivary gland; lymph node, inguinal; stomach; small intestine; large intestine; diaphragm; urinary bladder; eyes; testis; pituitary gland; peripheral nerve; brain; and bone marrow: No significant lesions.

VETERINARY PATHOLOGY REPORT

U.S. Army Medical Research Institute
of Chemical Defense
Aberdeen Proving Grounds, MD 21010-5425

11May99

ACCESSION NUMBER :
99-0391

(continued)
COMMENTS:

The cause of death in this case is attributed to generalized hepatic and renal failure resulting from diffuse and severe hepatocellular and renal tubular degeneration and necrosis. The hepatic and renal lesions are consistent with acute toxic injury, and are most likely the result of direct toxicity or biotransformation of the orally-administered experimental drug. However, we cannot completely rule out hypoxia as a contributing cause. The contribution of the heart lesions to the cause of death is probably not significant, but cannot be completely disqualified. The presence of hemorrhage in a variety of organs attests to a generalized coagulation deficiency, which is most likely secondary to compromised liver function. The cause of the acute necrosis of the zona reticularis in the adrenal gland is uncertian, but may also be the result of drug toxicity. This region of the adrenal gland is most sensitive to chemically-induced injury. The cause of the splenic congestion is not evident histologically, but may be related to passive congestion, agonal event, or increased splenic removal of altered erythrocytes. The esophageal lesions are consistent with chronic physical trauma, and may be the result of gavage procedures. The lesions from the skin samples collected from the inguinal region are consistent with the blunt trauma noted to that area clinically and during the post mortem examination. The other lesions are common incidental findings, and clinically insignificant.
The post mortem urinalysis revealed abnormally elevated levels of protein and a positive occult blood test. The elevated protein is consistent with lack of tubular resorption secondary to tubular damage. The positive occult blood test represents either an elevated presence of hemoglobin or myoglobin. In this case, the result is consistent with intratubular hemoglobin casts observed histologically.

REVIEWED BY:

Steven Duniho
Steven M. Duniho
MAJ, VC
Comparative Pathology Branch

Crystal M. Briscoe
Crystal M. Briscoe
MAJ, VC
Chief, Comparative Pathology Branch

DATE: 05/11/99

Appendix H. Purity Tests

Drug Purity

Mass Spectrometry

Conducted by:	Dr. Ming L. Shih and Mr. John R. Smith
Conducted on:	WR242511 and solvent samples
Dates conducted:	17-19 May 1999

Pyrogen testing

Conducted by:	Celsis Laboratory Group
Conducted on:	WR242511 and solvent samples
Dates conducted:	29-31 October 1998

Other purity tests

Conducted by:	SRI International (San Francisco, CA) via WRAIR (Mr. Bill Ellis, personal conversation, October 1999)
Conducted on:	WR242511 sample sent from USAMRICD to WRAIR on 1 September 1999
Dates conducted:	~October-November 1999

Appendix I. Pyrogen Testing Results

Celsis Laboratory Group

October 31, 1998

SUBMITTED TO: US Army/MRICD

ASSAY NUMBER: 820568

RECEIVED: 10/29/98

TEST MATERIAL: PEG 200
Lot/ID#: None

METHOD OF ASSAY: USP 23 <85> Bacterial Endotoxins Test

REAGENTS:
1. E. coli endotoxin ACC Lot 74 exp. 2/6/02 1000 EU/ml
2. Lysate (pyrotel) ACC lot 598-02-048 exp. 2/17/03 Sensitivity: 0.03 EU/ml
3. Positive Control: 0.06 EU/ml
4. Water: Biowhittaker LAL Reagent Water Lot 8M0864 exp. 5/11/00

RESULTS: (Endotoxin Standard)

(0.024 ng/ml) 0.12 EU/ml	+ +
(0.012 ng/ml) 0.06 EU/ml	+ +
(0.006 ng/ml) 0.03 EU/ml	+ +
(0.003 ng/ml) 0.0015 EU/ml	- -
(0.0015 ng/ml) 0.0075 EU/ml	- -
Positive Control	+ +
Negative Control	- -

Sample Dilutions	2 lambda spiked	Unspiked
1:10	- - - -	- -
1:20	+ + + +	- -
1:40	+ + + +	- -
1:80	+ + + +	- -

CONCLUSION: The sample contains <0.6 EU/mL active substance.

Work Approved by:

Anthony T. Grilli, M.S.
Director of Microbiology

New Jersey Division 165 Fieldcrest Avenue • Edison, New Jersey 08837 • 732 346-5100 • Fax 732 346-5115

Celsis Laboratory Group

October 31, 1998

SUBMITTED TO: US Army/MRICD

ASSAY NUMBER: 820569

RECEIVED: 10/29/98

TEST MATERIAL: Multisol
Lot/ID#: None

METHOD OF ASSAY: USP 23 <85> Bacterial Endotoxins Test

REAGENTS:
1. E. coli endotoxin ACC Lot 74 exp. 2/6/02 1000 EU/ml
2. Lysate (pyrotel) ACC lot 598-02-048 exp. 2/17/03 Sensitivity: 0.03 EU/ml
3. Positive Control: 0.06 EU/ml
4. Water: Biowhittaker LAL Reagent Water Lot 8M0864 exp. 5/11/00

RESULTS: (Endotoxin Standard)

(0.024 ng/ml) 0.12 EU/ml	+ +
(0.012 ng/ml) 0.06 EU/ml	+ +
(0.006 ng/ml) 0.03 EU/ml	+ +
(0.003 ng/ml) 0.0015 EU/ml	- -
(0.0015 ng/ml) 0.0075 EU/ml	- -
Positive Control	+ +
Negative Control	- -

Sample Dilutions	2 lambda spiked	Unspiked
Undil.	- - - -	- -
1:2	- - - -	- -
1:4	- - - -	- -
1:8	- - - -	- -
1:16	+ + + +	- -
1:32	+ + + +	- -

CONCLUSION: The sample contains <0.48 EU/mL active substance.

Work Approved by:

Anthony T. Grilli, M.S.
Director of Microbiology

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